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HABILITATION OF THE CLEFT-PALATE PATIENT

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DURING the last few years management of cleft palate has expanded rapidly and at the same time has become a very controversial field. It is no longer considered the sole province of the plastic surgeon, the prosthodontist or the speech therapist, but is recognized as an area demanding the co-operative efforts of multiprofessional teams. The collective information and knowledge of such integrated groups is gradually producing the necessary wisdom for successful care of the child with a cleft palate.

For many years, the majority of plastic surgeons have preferred to repair a cleft palate during the first two years of life, before the establishment of a speech pattern. It may be concluded from the literature that a vast group of surgeons and speech therapists believe that as operative age increases, the probability of achieving normal speech decreases. However, many orthodontists and prosthodontists and some surgeons consider it advisable to delay all surgery on the palate until a child is between four and seven years of age. Members of both the dental and medical professions have made cephalometric studies that have been interpreted to indicate that earlier surgery is detrimental to bone growth of the maxillary complex.[1-3] However, most of the factors that produce malocclusion in the general population also influence the facial growth of children with palatal defects. Since the standards used in cephalometric roentgenography are based upon statistical studies of ideal normals, comparison of data on cleft-palate patients with such ideal standards is no more valid than the comparison of similar data of patients without cleft palates with the same ideal normals.

The object of the present investigation is chiefly to evaluate the long-range results of surgical management and over-all care of children whose cleft palates were repaired at the Children's Medical Center in Boston. The study was motivated by the fact that clinical experience in this center has not found the bony distortions of the face that have been reported from other centers and interpreted as being due to early surgery. Also, it was believed that the children whose palates were repaired before the establishment of a speech pattern had speech results so good that continuation of the policy of early repair was certainly warranted.

In the past ten years, 1034 palatoplasties have been done in the Department of Plastic Surgery at the Children's Medical Center. This number includes only children receiving a primary one-stage closure of the palate; the vast majority of operations were done before two years of age. All the operations were performed by one surgeon, so that there was a planned uniformity of technic. The procedures had been developed and standardized well before the period included in this study. Thus, the surgery and the preoperative and postoperative care remained consistent, thereby eliminating as many variables as possible.

TIME AND METHOD OF REPAIR

For over twenty years it has been customary for us to repair a cleft lip when the baby has reached 2.7 kg. (6 pounds), is in good health, is gaining steadily and is five or six weeks of age. The cleft palate is repaired when the patient reaches 9.1 kg. (20 pounds), is in satisfactory condition and is approximately fourteen months of age. It has often been reported in the literature that operation on palate is repaired when the patient reaches 9.1 kg. risks.[4,5] The mortality in our group of 1034 palatoplasties has been 0 (and indeed it had been nil for quite some time before 1942).

The repair of all these cleft palates has followed a similar pattern. First, the edges of the cleft are freshened by excision of a narrow rim of tissue. Bilateral relaxing incisions are then made. These start outside the alveolar ridge of the lower jaw, extend across the commissure between the upper and lower jaw and then continue inside the alveolar ridge of

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the upper jaw running as far anteriorly as is thought necessary. In a complete cleft palate with alveolar defect, the anterior end of this incision usually stops just inside the lateral incisors. Mucoperiosteal flaps are then elevated, and the descending palatine vessels are isolated and carefully preserved. To obtain sufficient freedom of the palatal flaps, the vessels are stretched from their foramens, as robins pull angleworms out of a hole in the ground. Each hamulus is identified, and the tensor palatine muscles stripped off the end of it. The hamulus is broken and is angulated medially at its base. (It should be noted that on the few palates that have had a second operation for a V-Y lengthening, the hamulus is always found to have grown back into its original position and is easily identifiable.) The nasal mucosa with its fascial attachments is cut after it has been freed from the nasal surface of the palatal bones. The edges of the palatal cleft are then brought together with alternating single and mattress sutures of No. 00000 chromic catgut to the nasal surface and buccal surface. Plain catgut (No. 00000) is used for the submucosal portion of the uvula. It is believed that the success of a good repair depends largely on wide and extensive mobilization of the tissues so that there is no tension whatever on the palatal flaps, and, perhaps even more important, on extreme gentleness in the handling of this tissue. In every case the tongue is freed if it does not come out of the mouth easily. The tongue is lengthened by a horizontal incision of the frenulum and sutured in a vertical direction. Such liberation may be instrumental in giving good tongue-tip sounds.

Criteria for Successful Repair

The criteria for successful treatment of a cleft palate cannot be limited to the observations that complete palatal closure has been obtained any more than they can be based solely on such measures as cephalometric evaluation. The palatal closure should be complete and the cephalometric studies should show normal development, but above all else the child *must* be of acceptable appearance, speak well, within the limits of "normal speech," and be as well adjusted to life as his contemporaries.

Material for Study

Two groups of children, totaling 164, were chosen for follow-up study. The first comprised 108 private patients operated on between 1942 and 1952. From a much larger number of children with good speech, we selected these 108 because they lived within a 300-mile radius of Boston and could be brought back easily for study. The second group was drawn from a consecutive series of 75 private patients operated on in 1946 and 1947; of these, 56 were located and were available for study. To avoid cumbersome verbiage, this second group is called the "consecutive series." The statistical data gathered from this series is of interest when compared with that of the first or "selected group." We thought it important to try to determine why children with good speech have it. It was also important to learn in what proportion good speech developed after repair.

Dental evaluation was made of 164 patients. Because of the rigid standards for technic, cephalometric roentgenograms were satisfactory on only 112, which are reported below. Cephalometric examinations were also done on a random sample of the general population, and 25 children with neither palatal defects nor a history of any other defects were used for controls.

Method of Study

The children were classified according to age, sex and type of defect. To describe the anomaly a modification of the Veau classification was used.[6] However, for speech evaluation it is necessary to know simply if the child had a cleft of the soft palate alone, a complete cleft through the palate or a complete cleft of the palate and the alveolar ridge. Data were also obtained on the following points in each group: family history; age at time of lip repair; age at time of palate repair; preoperative adequacy of tissue, width of cleft, presence or absence of micrognathia and so forth; time of onset of speech and description of preoperative speech; analysis of present speech (a tape recording was made for each child); type of speech training, if any; velar length and activity; presence of Passavant's ridge or lateral pharyngeal activity or both; audiometric evaluation; status of ear, nose and throat, including time of tonsillectomy and adenoidectomy and any postoperative nasality thereafter; cephalometric roentgenographic examination; occlusal evaluation by casts and intraoral x-ray studies; estimate of child's intelligence and general adjustment; and estimate of adequacy of home environment.

To describe speech, the following classification was used:

Normal, non-nasal speech.

Non-nasal speech with minor articulatory defects: the articulatory defects included here are of the type not secondary to a cleft palate, such as lalling, lisping or infantile sound substitutions.

Slight nasality: nasality to such a slight degree that the casual listener would not be concerned over it.

Moderate nasality: to the extent that anyone would notice it.

"Cleft-palate speech": severe nasality and the type of faulty articulation commonly attributed to an unoperated or poorly repaired cleft palate (rhinolalia aperta).

Hyponasal speech: markedly blocked or "adenoidal" in quality (rhinolalia clausa).

Although such speech evaluation is purely subjective, it has been proved to be an acceptable scale in over-all clinical evaluation of the child with a cleft palate. Further analytic research based on objective data, such as correlation of measured radiologic and laminographic findings with type of speech,[7] is beyond the scope of this presentation.

A tape recording was made of each child's speech. The child was asked to repeat 10 or 12 sentences chosen to illustrate particularly the sibilants (s, z, sh, zh) and plosive consonants (k, g, t, d, p, b, tch, dge). To demonstrate the presence or absence of nasal emission of breath during speech, the child was asked to repeat the sentence, "Bobby had a lazy old cat"; this was done normally and also while he was holding the nose.

To check our judgment of "normal" speech a test tape was made containing the voices of 20 children; some of these had had a cleft-palate repair, and some were normal children. This tape was then presented as a test to the Surgical House Staff, to a group of graduate students in the Department of Speech Pathology at Boston University and to the members of the New England Pediatric Society. The listeners were requested to identify children who had repaired cleft palates and those who were normal. In each test many of those taking the test could not tell the difference. Some of them called normal children "cleft palate" and some also called children with cleft palates "normal." The results were no better than chance guessing; the majority of listeners agreed that all the children on the tape had speech within the range of normal limits.

Dental examination included occlusal evaluation by means of casts and intraoral x-ray examinations as well as cephalometric roentgenography. The latter basically involves a special device by means of which the head can be held in a fixed position during the exposure of the film. Since any method of immobilizing the skull is hampered by the soft tissues that overlie the bony parts, some variation is possible but can be minimized with proper technic. In this study a Margolis cephalostat was used.

Results

General Data

The general data for both groups are outlined in Table 1. It may be noted that some of the children are listed as having a "questionable" family history of palatal defect. It is found that, although many parents know of no family history of cleft lip or cleft palate, some of them report variations in the manifestation of the syndrome of cleft lip and cleft palate.[8,9] Such items included congenital cleft-lip scar, velar insufficiency, excessively high palatal vault and absent uvula. Among the related orodental anomalies reported were supernumerary teeth, suppression of one or more incisors and irregularity of the dental arches.

Table 1. *General Data.*

Source of Data	Total Patients	Average Age	Sex Ratio (Male:Female)	Patients with Positive Family History	Patients with Questionable Family History	Average Age at Time of Operation	Patients Operated on by 2 Yr. of Age
		yr.				*mo.*	
Selected group	108	7½	1:1	22 (20%)	21 (19%)	19	91 (84%)
Consecutive series	56	9	2:1	10 (18%)	7 (12%)	17	49 (87%)

The children in the selected group ranged in age from three to seventeen years, the mean age being seven and a half years, and those in the consecutive series from seven to thirteen years, the mean age being nine years. The average age at operation in the selected group was nineteen months, and that in the "consecutive series" seventeen months; 84 per cent of the children in the selected group were operated on before twenty-four months of age, and 50 per cent of them were operated on by fifteen months. Of the consecutive series, 87 per cent were operated on before twenty-four months and 50 per cent at fourteen months of age.

Type of Defect

To determine the possible relation between type of cleft and the postoperative result, it would be helpful to know not only the extent of the unoperated cleft but also the width of the defect, adequacy or inadequacy of palatal and velar tissue, presence or absence of micrognathia and so forth. All such information was rarely available from the records in sufficient detail to provide a clear preoperative picture. Therefore, the cleft palate was classified according to its location on an anteroposterior plane, which admittedly is inadequate description at best. Table 2 shows the distribution of the types of cleft palate; the numerals refer to those of the Veau classification.[6] In the selected group 56 (52 per cent) were postalveolar clefts, and 52 (48 per cent) were per-alveolar. In the consecutive series, 20 (36 per cent) were postalveolar and 36 (64 per cent) were per-alveolar clefts.

Speech Results

Speech results are shown in Table 3. Eighty-three per cent of the children in the selected group and 71 per cent of those in the consecutive series had no na-

sality and no nasal emission of breath during speech. The majority of articulatory defects were lisping or lalling (substitution of W for R or L), the latter bearing no relation to any palatal or dental condition. As would be expected, most articulatory defects involved the sibilants and occurred in the children with alveolar cleft. The majority of these will show considerable improvement after orthondontia whether they receive speech therapy or not. This is especially true of the children who have normal voice quality.

TABLE 2. *Type of Distribution.*

TYPE OF DEFECT*	PATIENTS IN SELECTED GROUP	PATIENTS IN CONSECUTIVE SERIES
I	13	2
II	37	16
III	39	23
IV	15	12
Cleft lip + II	2	2
II through alveolus	1	1
Cleft lip + alveolus + uvula	1	0
Totals	108	56

*Modified Veau classification.[4]

It is noteworthy that consistently the parents of the children who now have normal speech stated that the primary speech problems encountered were articulatory. None of this group reported nasality to be a problem in speech development.

Velar Length

Velar length was observed clinically and was simply described either as relating to a palate that appeared

TABLE 3. *Speech Results.*

TYPE OF SPEECH	PATIENTS IN SELECTED GROUP	PATIENTS IN CONSECUTIVE SERIES
Normal non-nasal	76 (70%)	28 (50%)
Non-nasal with faulty articulation	14 (13%)	12 (21%)
Slight nasality	12 (11%)	6 (11%)
Moderate nasality	4 (4%)	1 (2%)
Hyponasal	2 (2%)	1 (2%)
"Cleft palate"	0	8 (14%)
Totals	108	56
Total non-nasal cases	90 (83%)	40 (71%)

too short to effect velopharyngeal closure or one that appeared adequate to effect closure, all other factors being equal. Table 4 shows these results. Of the total of 130 children with no nasality, 46 per cent had soft palates that were considered too short to permit a "normal" velopharyngeal closure. This was true of 70 per cent of the total of 34 children with nasal speech, including the 8 with "cleft-palate speech." In view of all other factors, the relation between nasality and velar length is not statistically significant in these cases. Although clinical appraisal allows only a rough estimate of velopharyngeal closure, results of clinical radiographic and laminagraphic studies reported elsewhere corroborate these findings.[10-16]

Lateral Pharyngeal Activity

Because of the large number of variables implicit in speech development itself, it is difficult to analyze the reasons for good speech. Major emphasis in the literature to date has been placed on the levator sling, Passavant's ridge and the musculature involved in achieving velopharyngeal closure. The functional anatomy of the palate and pharynx has been described by many observers on the basis of anatomic dissection, direct observation and roentgenology. The majority agree that this is a "complex patterning of interaction between the horizontal, vertical and oblique muscular fibers of the nasopharynx, oropharynx and palate."[17] Observation of the children with non-

TABLE 4. *Relation between Type of Speech and Velar Length.*

TYPE OF SPEECH	PATIENTS IN SELECTED GROUP		PATIENTS IN CONSECUTIVE SERIES	
	SHORT VELUM	ADEQUATE VELUM	SHORT VELUM	ADEQUATE VELUM
Normal non-nasal	34	42	7	21
Non-nasal with faulty articulation	9	5	9	3
Slight nasality	7	5	3	3
Moderate nasality	4	0	1	0
Hyponasal	0	2	1	0
"Cleft palate"	0	0	8	0
Totals	54	54	29	27
Total with any nasality	11	7	13	3

nasal speech in both the selected group and the consecutive series revealed one outstanding factor. When the oropharynx was examined while the child was saying "ah," *without exception* every child with non-nasal speech exhibited marked inward movement of the lateral pharyngeal walls. The posterior faucial pillars seemed to leap toward each other. This was true of the three-year-olds as well as of the older children and was in no way related to the length of the velum. The following held true in *every* case:

Non-nasal speech resulted if the palate was long and muscular and there was good lateral pharyngeal activity, with or without strong visible contraction of the posterior pharyngeal wall, or if the palate was short but there was tremendous lateral pharyngeal activity, with or without strong visible contraction of the posterior pharyngeal wall.

Slight or moderate nasality occurred if the palate was short and lateral activity was weak.

"Cleft-palate speech" resulted if the palate was short and lateral pharyngeal activity was absent.

The findings of this study suggest that the palatopharyngei and the salpingopharyngei may play a more

active part in the development of good speech in the child with cleft palate than has been realized before. The action of these muscles normally is to decrease the breadth of the pharyngeal isthmus and, acting in the reverse direction, to elevate the posterolateral pharyngeal walls, thereby promoting or facilitating contraction of the superior constrictor at the level of Passavant's ridge.[18] Wardill,[19,20] Subtelny[21] and others[14] have concluded that the lateral dimensions of the nasopharynx are wider in persons with cleft palate. The lateral pharyngeal activity exhibited by the non-nasal speakers seen in this study indicates that there is considerable compensatory activity to diminish the isthmus on a transverse axis. It is significant that, of the children followed, those with good speech showed greater movement of the lateral wall than is seen normally or than was observed in children with nasality.

It is also noteworthy that, of the non-nasal speakers, the high-riding tongue reported by many as being typical of the child with cleft palate was not observed.[22-24] These children showed no humping of the dorsum of the tongue; lingual motility was excellent.

Hearing

The audiometer used was an ADC, Type 50E. Testing was performed in a sound-treated office under uniform conditions. Each child was screened at 15 decibels, but if any one frequency was missed, a thorough audiometric test was given. All those with an average loss of 20 decibels or more in the better ear are reported as having hearing loss (19 per cent of the entire group).

Of the selected group 23 (21 per cent) had hearing loss. Eleven were males, and 12 females. Twelve had unilateral loss — 10 on the left, and 2 on the right. Eleven had bilateral loss. As grouped according to type of defect, 8 were in Class II (Veau), 10 in Class III and 5 in Class IV.

TABLE 5. *Distribution of Hearing Loss According to Type of Speech (Selected Group).*

TYPE OF SPEECH	NO. OF CASES	TYPE OF HEARING LOSS
Normal non-nasal	16	None greater than 40 decibels
Non-nasal with faulty articulation	4	Right — 0 Left — 38 decibels Bilateral — 30 decibels Bilateral high frequency — 65 decibels
Slight nasality	1	Bilateral — 20 decibels
Moderate nasality	2	Right — 30 decibels Bilateral — 30 decibels

In the consecutive series 8 (14 per cent) had hearing loss. Seven were males, and 1 female. Five had unilateral loss — 4 on the left, and 1 on the right. Two had bilateral loss. As grouped according to type of defect, 3 were Class II (Veau), 3 Class III, and 2 Class IV.

These figures are much lower than those reported elsewhere.[4,25-27] Sataloff and Fraser,[27] for instance, reported the highest incidence; in a group of 30 children, 90 per cent had hearing loss of at least 15 decibels in at least two frequencies. Such criteria, however, are stricter than those adopted for most studies. The expected figure for children with cleft palates who have hearing loss generally is at least 25 per cent.[4]

Table 5 shows the distribution of hearing loss according to type of speech for the selected group, and Table 6 that for the consecutive series. Of the total number with hearing loss, the majority were in the range of 30-40 decibels. Except for 3 children, who possibly have a congenital nerve deafness, the most severe impairment was a unilateral loss averaging 50 decibels in the speech range, and the type was characteristically conductive.

TABLE 6. *Distribution of Hearing Loss According to Type of Speech (Consecutive Series).*

TYPE OF SPEECH	NO. OF CASES	TYPE OF HEARING LOSS
Normal non-nasal	3	Left— 50 decibels Bilateral — 20 decibels Bilateral — 35 decibels
Non-nasal with faulty articulation	3	Left — 0 Right — 20 decibels Bilateral — 35 decibels
"Cleft palate"	2	Left— 36 decibels Left— 60 decibels

Time of Onset of Speech

The relation between the time of onset of speech (whether preoperative or postoperative) and type of speech is of no significance in this study since the average operative age of these children is well under two years. To be significant, results such as these must be considered in relation to those of a similar study of children operated upon at a much older age. It is of interest that 98 per cent of the children showed no delay in onset of speech and were speaking in sentences by the age of thirty months.

Type of Speech Training

Of the total of 164 children, there were 130 who had no nasality (79 per cent of the entire group). Of the 130, there were 116 (90 per cent) who had no speech training other than that provided by parental guidance — that is, they had no formal speech therapy. Other children in the study received professional speech therapy ranging from periodic preschool checkups to weekly lessons carried through their school careers to date. Tables 7 and 8 show the relation between speech training and type of speech in the two groups.

When the figures for the consecutive series are broken down and plotted according to presence or absence of any nasality versus presence or absence of

any formal speech therapy, the difference between the percentages as tested by χ^2 (chi square)* is significant. Thus, it is highly significant statistically that 72.5 per cent of the children with no nasality in the consecutive series had no speech training other than by the parents.

The parents were thoroughly instructed to give the child blowing exercises and to carry out a good deal of ear training beginning one month after the palatoplasty. At the age of three or four years each child was seen by our speech therapist, who determined the necessity for specialized training and who counseled the parents as indicated. Until this time, the parents were instructed to read to the child, look through picture books and play "speech games" daily. Particular attention was placed from the start on the most difficult sounds (c, k, s and t). Provision of an environment conducive to and productive of good speech development was emphasized; this includes good speech models and good speech standards in the home, adequate stimulation for self-expression and opportunity for a good deal of listening as well as for building vocabulary and so forth. The most diligent group of parents were those whose children had the best speech, and the majority of these were regarded by the speech therapist as having normal speech at the age of three or four years.

TABLE 7. *Relation between Type of Speech and Speech Training (Selected Group).*

Type of Speech	Patients Receiving Parental Guidance	Patients Receiving Professional Therapy Only			Patients Receiving No Help
		Preschool	School	Both	
Normal non-nasal	75	1			
Non-nasal with faulty articulation	12				2
Slight nasality	4		1		7
Moderate nasality	1			3	
Hyponasal	2				
Totals	94 (87%)	5 (45%)			9 (8.5%)

TABLE 8. *Relation between Type of Speech and Speech Training (Consecutive Series).*

Type of Speech	Patients Receiving Parental Guidance	Patients Receiving Professional Therapy Only			Patients Receiving No Help
		Preschool	School	Both	
Normal non-nasal	24	3			1
Non-nasal with faulty articulation	5	1	2		4
Slight nasality	4	1		1	
Moderate nasality			1		
Hyponasal	1				
"Cleft palate"			3	4	1
Totals	34 (61%)	16 (29%)			6 (10%)

*$\chi^2 = \Sigma \frac{(\text{Observed results} - \text{expected})^2}{\text{Expected results}}$.

Cephalometric Examination

The cephalometric x-ray studies were evaluated according to the analysis of Downs[28] as modified by Baum,[29] in which an attempt is made to appraise the facial pattern by means of angular measurements. These measurements show the relation of the teeth, alveolar processes, maxilla and mandible to each other as well as to the cranium.

FIGURE 1. *Summary of Cephalometric Findings. Solid line indicates 112 patients with cleft palate, broken line Downs's ideal normals, and dotted line 25 unselected controls.*

Three cephalometric x-ray examinations were made on each patient. Nine angular measurements were made on each film. To describe each one and to discuss its significance are beyond the scope of this presentation. A detailed report is now being compiled with special emphasis on these dental aspects.

Figure 1 graphically summarizes the cephalometric findings. The three tracings represent the mean values for 112 patients with cleft palate (solid line), Downs's ideal normals (broken line) and 25 unselected children to serve as controls (dotted line). These tracings represent angular projections rather than linear measurements.

The statistical means for the angular measurements relating the mandible to the cranium were constantly similar in all classes (Veau), the greatest individual variation being found in Class IV patients. The mean for the axial inclination of the maxillary central incisors is based upon 79 patients. The remaining 33 patients had no central incisors (group between six

and seven years of age) or had had teeth removed. Still others had teeth so completely rotated and overlapping that the axial inclination could not be determined with accuracy. The total number of teeth in crossbite per patient was surprisingly low.

Occlusal Evaluation

Mirror-explorer examinations, dental casts and intraoral x-ray examinations were the methods used to appraise the functional effectiveness and appearance of the teeth.

Of the 42 Class I and II patients, 6 were found to have ideal occlusions, and adequate occlusions were observed in all but 7. Five of these 7 had crowding because of premature loss of deciduous teeth.

Crossbite relations of teeth are the most frequent dental irregularity seen in patients with cleft palate and also a common irregularity in the general population. A crossbite is the term used to describe an upper tooth or teeth biting inside the lower arch. The distribution of teeth found in crossbite relation in the 112 patients studied is shown in Table 9.

Many patients in Class III were found to have minor malocclusions that could be corrected orthodontically. Some others had severe malocclusion requiring more extensive orthodontic measures. To reduce these malocclusions to exact figures seemed undesirable since orthodontic diagnosis and prognosis are unpredictable in any group of cleft-palate patients. Supernumerary teeth, as well as congenital absence of dental units, were commonly associated with the lateral-incisor areas in Class III and IV patients. Only 1 patient of the 42 in Class I and II had a missing lateral incisor.

Dental care varied considerably, many having received good dental care from the beginning and others having been sadly neglected. In the latter group, the neglect was usually due to the refusal of the local dentist to accept responsibility for routine dental care.

Environment and Adjustment

The families of all the children in both groups were of good socioeconomic level. Only 2 were children of divorced parents, and, on the whole, the families functioned adequately as integral groups.

At present the children seem to be of good intelligence and doing average or better work at school. The majority have been active in group life in their schools and communities and are outgoing, well adjusted youngsters.

Discussion

The findings of this study add further question to the validity of the assumption that nasality is a direct result of an inadequate cleft-palate repair and that normal speech should result with adequate velopharyngeal closure. Russell[11] pointed out many years ago that an opening into the nose does not necessarily mean nasality of tone: "It is only when the tone is penned in, in some sort of cul-de-sac, that it turns out to be what is called nasal in quality." He went on to show that excessive constriction produced by the epiglottis, by the interior larynx or between the tongue and the walls of the pharynx may cause the lower pharyngeal cavities to form such a cul-de-sac. This may also be true of the speaker who makes high back contacts of the tongue with the hard palate and velum.[14,23,24]

It has been found that the velopharyngeal space may be of any width without producing nasality, provided that the minimal tubular area of the anterior nasal passage is greater than the posterior one. Nasality will result if the labial opening is smaller than either nasal opening or, as Kaltenborn[15] concluded, if there is "too wide an opening into the nasopharynx in comparison with the opening into the nasal cavity."

Table 9. *Distribution of Teeth Found in Crossbite Relation.*

Veau Classification	No. of Patients	No. of Patients with Crossbite	Percentage of Patients with Crossbite	Total No. of Anterior Teeth in Crossbite	Total No. of Posterior Teeth in Crossbite
I	8	1	12.5	2	0
II	34	9	26.5	6	4
III	69	50	72.4	105	79
IV	11	11	100.0	26	25

The activity of the lateral pharyngeal wall observed in the non-nasal speakers in this study must act, at least in part, as a compensatory mechanism to ensure that the width of the nasopharyngeal cavity is not larger than the opening into the nasal cavity and that the labial opening maintains its respectively larger dimension. That these children showed no lingual bulging or humping during phonation and had unobtrusive, mobile tongues may be included as an important factor in their lack of nasality. Whether the practice of lengthening the lingual frenulum at the time of palatoplasty contributes to lingual motility in these cases is difficult to conjecture.

Enough data have been presented in the literature to indicate that nasality is related to many factors other than velopharyngeal closure, especially to the acoustic factors pertaining to cavities and cavity coupling.[11,14,30-34] When one thinks of the quality of cleft-palate speech, instead of concentrating solely on any single factor, it appears necessary to think in terms of an acoustic phenomenon involving the physiologic sound filter and the cavity relations in the entire pharyngeal area. This includes consideration of tongue and mandible positions and the degree of patency of the oropharynx, as well as the relation of the buccal, pharyngeal and nasal cavities.

It was clearly demonstrated during the course of the present study that the best speech results were obtained when the child's palate was closed before the establishment of a speech pattern and when he

had been brought up, from infancy, in an environment enabling him to have every possible assistance in his speech development. The homes of these children with normal speech provided adequate motivation and stimulation for speech, good speech models and a great deal of ear training. When such parental guidance is unobtainable, it seems advisable to engage a professional speech therapist for counseling and guidance, preferably before the child is three years old. The need for such early guidance is being recognized in other cleft-palate centers. McWilliams[35] even suggests that the speech therapist should begin supervision of the child's speech environment at birth. The fact that the parents of the non-nasal speakers in this study found that their children needed help with articulation rather than nasality lends support to the emerging practice of directing speech therapy more strongly toward articulation.[36,37] Certainly, it has become apparent that to delay some form of speech guidance beyond the age of two years is to impair the child's chances for normal speech. This study has shown much evidence that surgical closure of the palate before the age of two years is of considerable benefit. Without an intact articulatory mechanism it is doubtful if the child could reap the full benefit of his speech training.

From the standpoint of appearance, a critical appraisal of the "skeletal profile" revealed harmonious relations among the various bony landmarks. The prognathic chin point and concave profile are therefore not characteristic of this group. Persons were seen whose facial balance was less favorable. Deviation of the nose and deficiency in bulk of the upper lip, with or without proper support from permanent incisors, coupled with a well developed lower lip, can also alter the profile. Thus, the soft tissues may camouflage an adequate skeletal pattern, especially in Class IV patients. It should be pointed out that when orthodontic treatment is indicated harmony of the facial skeleton is essential for a favorable prognosis. When the cephalometric results were analyzed and projected in the form of a facial outline, there were striking differences between the outline for the group of cleft-palate patients and the outline representing the *ideal* normal standards. These same differences were observed when the *average* normal was compared with the *ideal* normal. When the patients with cleft palate were compared with the *average* normal controls, no statistical difference could be demonstrated. The frequency of ideal and adequate occlusions found in Class I and II patients certainly indicates that no major impairment of growth and development of the maxillary complex had resulted from early surgical intervention.

It would be impossible to correlate the common finding of crossbite in Class III and IV patients with the time of surgery until the figures could be compared with those from a series of patients operated on at an older age. The presence of an intact alveolar ridge in the Class I and II patients seemed to prevent mesial collapse and also seemed to be of paramount importance in the development of a satisfactory occlusion.

Summary and Conclusions

During the past ten years a total of 1034 children were operated upon for cleft palate by the Plastic Service of the Children's Medical Center in Boston. From this larger number two groups totaling 164 were seen for a detailed follow-up study. The average operative age of the entire group was nineteen months. All were operated upon by the same surgeon. Fifty-six of the children represented a consecutive series operated upon in 1946 and 1947. The remaining children (108) were selected because of good speech and availability.

Of the entire group, 130 (79 per cent) spoke with no nasality, and, of this number, 116 (90 per cent) had no speech therapy other than that given by parental guidance. Only 19 per cent of the entire group had a hearing loss averaging at least 20 decibels in the better ear.

Activity of the lateral pharyngeal walls appeared to be the most important single factor in the physical production of good speech. Of no discernable significance was the type of original cleft, length of palate, and hearing loss.

One hundred and sixty-four children received thorough dental examination. Facial patterns as determined by cephalometric evaluation were different from ideal normal patterns, but did not differ appreciably from those of a random sample of the normal population. Dental occlusions were good in a number of patients and ideal in some whose defects did not extend through the alveolar process. Crossbite relations found in unilateral and bilateral alveolar cleft palate were common but cannot be related to the time when the operation was performed.

In this study it has been shown that an early and proper surgical repair, coupled with intelligent parental speech guidance and conscientious dental care achieves satisfactory habilitation of the child with a cleft palate, thereby avoiding the need for *re*habilitation.

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ELECTROCARDIOGRAPHIC AND BLOOD-PRESSURE CHANGES DURING AND AFTER BILIARY-TRACT SURGERY*

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PHILADELPHIA

THE association of biliary-tract and coronary-artery disease has been noted clinically for many years.[1-14] This relation has been investigated extensively in the laboratory. There have been repeated references to reflexes arising from the upper abdominal viscera and especially the biliary tract that could give rise to cardiac arrhythmias, a reduction in coronary blood flow and even catastrophe during surgery of the biliary tract.[13,15-21] However, the work of several investigators failed to reveal any consistent significant electrocardiographic changes related to manipulation of this area.[22-28] In the laboratory animal varied changes in coronary blood flow and in the electrocardiogram that were due to visceral manipulation or distention have been reported.[15,17,-19-21]

The decrease in coronary blood flow in laboratory animals was thought by some investigators to be due to coronary constriction mediated by way of the vagus. Others believed that any reduction in coronary flow caused by biliary-tract distention or direct stimulation of the vagus was secondary to a fall in blood pressure. Eckenhoff and his co-workers,[30-32] in fact, considered the coronary vessels in dogs to possess an effective intrinsic control of coronary flow mediated by metabolic needs, and they were unable to demonstrate any effective vasomotor control over the coronary circulation under the conditions of their study.

It occurred to us that an objective study of the cardiac and circulatory status of patients undergoing biliary-tract surgery might reveal the presence of cardiovascular changes due to abdominal manipulation that could conceivably be missed by the anesthesiologist, surgeon and internist using present clinical methods of observation.

TABLE 1. *Age Distribution.*

AGE	NO. OF PATIENTS
yr.	
20-29	2
30-39	3
40-49	7
50-59	16
60-69	12
70-79	7
80-89	3

METHODS AND MATERIALS

Fifty patients, whose ages ranged from twenty-four to eighty-one years and who were undergoing biliary-tract or upper abdominal surgery, were studied (Table 1). A large number of these patients had

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operative cholangiograms, which required that the common duct be dilated to varying degrees. The series included 30 patients known preoperatively to have cardiac disease and 20 patients with no history or demonstrable evidence of cardiac disease. Most of them had a history of cardiac disease because it was thought that in this group abdominocardiac reflexes would be more likely to develop since it has been shown[18,19,28,33,34] that significant reflex changes in coronary blood flow and electrocardiogram occur more frequently in previously damaged hearts. The cardiac group consisted of 12 patients with arteriosclerotic heart disease, 10 patients with hypertensive cardiovascular disease and arteriosclerotic heart disease, 7 with hypertensive cardiovascular disease and 1 patient with an undiagnosed acyanotic congenital heart lesion (Table 2).

TABLE 2. *Preoperative Cardiac Status.*

GROUP		NO. OF PATIENTS
Patients with no heart disease		20
Patients with heart disease		30
Arteriosclerotic heart disease	12	
History of previous infarction	3	
Hypertensive cardiovascular disease	7	
Arteriosclerotic heart disease & hypertensive cardiovascular disease	10	
History of previous infarction	4	
Acyanotic congenital heart disease	1	

Twelve-lead electrocardiograms were recorded preoperatively on all patients. During surgery Lead V_4 was followed with reference to the limb leads at intervals. Electrocardiograms were taken during the immediate postoperative period when the patient had reacted from the anesthetic. Follow-up electrocardiograms were done at varying intervals postoperatively.

In 45 cases, the brachial artery was cannulated, and continuous pressure pulses were recorded with the use of a Statham transducer. These were recorded simultaneously with the electrocardiogram by means of a Sanborn Twin-Viso Cardiette.

The patients received premedication consisting of morphine or Demerol and atropine, with dosages varying according to age, weight and physical status.

In 46 cases, anesthesia was maintained by a combination of thiopental (Pentothal Sodium), nitrous oxide and succinylcholine chloride.* After induction with thiopental and succinylcholine, endotracheal intubation was performed, and the patients were maintained on controlled respirations with the use of nitrous oxide and oxygen supplemented by intermittent doses of thiopental and succinylcholine when indicated. At least 25 per cent oxygen and frequently larger amounts were administered at all times. The patients were maintained in a light plane of anesthesia. In 2 cases, cyclopropane with succinylcholine as the relaxant was used after intubation with thiopental and succinylcholine. Ether was used in 1 case. Gallamine triethiodide (Flaxedil) was the relaxant in 1 case.

*Kindly supplied as Anectine by Burroughs Wellcome and Company, Incorporated, Tuckahoe, New York.

RESULTS

Of the group of 20 patients with no clinical evidence of cardiac disease preoperatively, 5 (25 per cent) showed variations in pulse or blood pressure that were related to surgical manipulation. There were no electrocardiographic changes except sinus bradycardia due to surgical manipulation. Reversible blood-pressure drops, the most significant of which was from 158 systolic, 104 diastolic, to 102 systolic, 80 diastolic, occurred in 2 patients. A sudden rise in blood pressure associated with manipulation (90 systolic, 68 diastolic, to 158 systolic, 102 diastolic) occurred in 1 patient. Six patients (30 per cent) with no cardiac disease had gradual electrocardiographic changes that could not be ascribed to any specific surgical maneuver such as gall-bladder manipulation. These changes were not related to variations in blood pressure except possibly in 1 patient in whom a rise in blood pressure was accompanied by tall, peaked, symmetrical T waves. Transient, tall, peaked, symmetrical T waves were recorded in 3 cases. Transient ST-segment changes occurred in 1 case, and in another flattened T waves and ST-segment depressions developed but disappeared as surgery progressed. Ventricular premature beats were seen in 1 patient.

Of the group of 30 patients with cardiac disease preoperatively, changes related to surgical manipulation developed in 15 (50 per cent). Alterations in the electrocardiogram other than sinus bradycardia occurred in 5 patients. These changes were atrioventricular dissociation, atrial premature beats with lowered T waves, increased frequency of ventricular premature beats and recurrence of a preoperative transient left-bundle-branch block associated with a mechanical alternans and aberrant QRS complexes. Transient sinus bradycardia occurred in 5, and a fall in blood pressure not associated with pulse changes in 4 cases. One patient had a sudden rise in blood pressure. All these changes bore a temporal relation to surgical manipulation that suggested that they were reflex.

Twenty-two (73 per cent) patients with cardiac disease manifested gradual electrocardiographic changes that could not be ascribed to any specific surgical manipulation. With the exception of 1 case, these changes could not be related to changes in blood pressure. During operation, the electrocardiograms in 8 cases showed significant improvement, involving ST-segment and T-wave changes. These were definitely related to slowing of the pulse rate in 3 cases. ST-segment abnormalities and flattened or inverted T waves occurred in 5 cases. Flattened T waves alone developed in 3, and tall, peaked, symmetrical

T waves in 2 cases. Inverted U waves occurred in 1. One patient manifested an atrioventricular dissociation with secondary ST-segment and T-wave changes (Fig. 1). In this case a myocardial infarction subsequently developed. Atrial premature beats were seen in two cases.

Significant hypotension during surgery occurred in only 2 cases. An eighty-year-old man with hypertensive cardiovascular disease had a drop in arterial blood pressure from 190 systolic, 110 diastolic, to 48 systolic, 30 diastolic, at the start of operation. There was no change in pulse rate or electrocardiogram during or after this hypotensive episode. A gradual, extreme rise in blood pressure — from 136 systolic, 74 diastolic, to 220 systolic, 124 diastolic — was observed in 1 case without accompanying electrocardiographic or pulse-rate changes. One patient, whose preoperative blood pressure was 220 systolic, 90 diastolic, had a fall in arterial blood pressure from 240 systolic, 113 diastolic, to 187 systolic, 90 diastolic, with concomitant flattening of the T waves. With the gradual return of blood pressure to the preoperative level, the T waves became upright.

Improvement in the immediate postoperative electrocardiogram, as compared with the immediate preoperative tracing, was recorded in 4 cases. Nine patients had electrocardiographic evidence of myocardial ischemia — that is, changes in ST segments and T waves — in the immediate postoperative period in the presence of high oxygen concentration with little or no change in blood pressure. It is significant that of the 9 patients with evidence of ischemia, 4 (2 with ST-segment depression, 1 with ST-segment elevation and 1 with ST-segment depression followed by elevation) went on to the development of electrocardiograms consistent with the diagnosis of myocardial infarction (Fig. 2, 3 and 4). One infarct involved the inferior aspect of the left ventricle. Significant Q waves were present. Three patients showed T-wave changes compatible with the diagnosis of anterolateral infarction, but lacked unequivocal diagnostic Q waves. These T-wave changes persisted for two months or more. Four of the remaining patients reverted to their preoperative electrocardiographic status within two or three days of operation. The remaining patient was discharged with an electrocardiogram that suggested myocardial ischemia but could not be classified as showing an infarction.

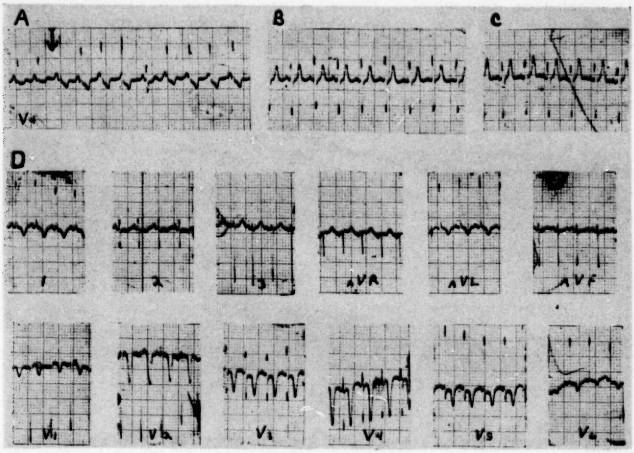

FIGURE 1. *Electrocardiograms in Case 3, a Sixty-Year-Old Woman with a Preoperative History of Hypertension and Preoperative Electrocardiograms Showing a Nonspecific Abnormality (Paper Speed, 10 Mm. per Second).*

In A (Lead V_4) *arrow points to onset of atrioventricular dissociation simultaneously with traction on the gall bladder; this persisted for about twenty minutes and reverted spontaneously.*

In B (Lead V_4) *note the appearance of tall, symmetrical peaked T waves that appeared about twenty seconds from the end of the atrioventricular dissociation.*

In C (Lead V_4), *the tracing taken immediately after operation, the T waves are taller than the QRS complex. In* D, *the electrocardiogram taken on the ninth postoperative day, the T waves are inverted in Leads 1, 2, aVL and V_3 through V_6. There is slight ST-segment depression in Leads V_3 through V_5 — these changes persisted for approximately eight weeks.*

DISCUSSION

The rate of occurrence (8 per cent) of myocardial

infarction in this series was surprisingly high, especially since these patients appeared to be doing well clinically during operation and in the postoperative period. The infarctions all occurred in patients known to have cardiac disease, but not necessarily in those who were the poorest risks. Two patients had histories of previous infarction. None of the causes of postoperative infarction usually postulated were present in this group. There was nothing peculiar to these patients, either preoperatively or during surgery, to distinguish them from the other cardiac patients except that their immediate postoperative tracings were suggestive of myocardial ischemia or infarction in their respective institutions. Wroblewski and LaDue[36] estimate the incidence to be less than 1 per cent. We believe that this does not represent the true incidence of postoperative myocardial infarction, since the diagnosis is undoubtedly overlooked in a number of "silent" cases. Our figure probably does not represent the true picture since our series was not derived from consecutive cases but from cases picked because of poor preoperative status. However, we think that the number of unsuspected infarctions in our series warrants the conclusion that closer electrocardiographic scrutiny of cardiac patients after operation is essential.

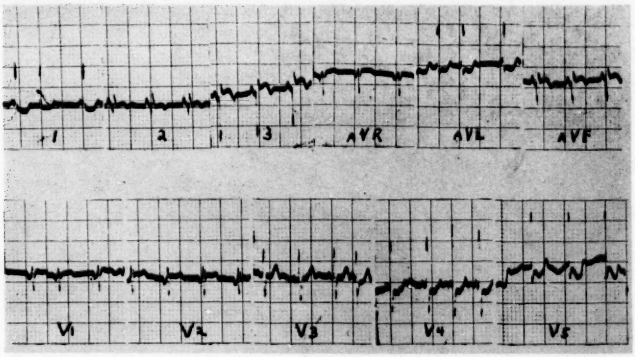

FIGURE 2. *Electrocardiograms in Case 29, a Fifty-seven-Year-Old Woman with a History of Myocardial Infarction about Two Months before Surgery and Preoperative Electrocardiograms Showing a Nonspecific Myocardial Abnormality (Paper Speed, 10 Mm. per Second).*

The electrocardiogram taken on the fourth postoperative day is consistent with an acute inferior infarction.

infarction and that the follow-up electrocardiograms were consistent with myocardial infarction.

The 5 patients with similar tracings suggestive of ischemia immediately after operation did not subsequently have evidence of myocardial infarction. None of those in whom infarction developed had clinical manifestations during the postoperative period that led the attending physicians to suspect serious cardiovascular complications. This was probably due to the presence of pain at the operative site, the elevated threshold to pain and dulled sensorium because of the routine use of narcotics and the relative inactivity of these patients during the postoperative period, as reported by other investigators.[35,36]

The frequency of unsuspected myocardial infarction in this series has led us to believe that this complication probably occurs more frequently than has been previously realized. It is not believed that it is specific to biliary-tract surgery or to the type of anesthesia used. Further investigation may clarify this point.

Master et al.,[35] Wroblewski and LaDue[36] and, more recently, Wasserman, Bellet and Saichek[37] reviewed the recognized cases of postoperative myocardial in-

The effect of biliary-tract manipulation on the electrocardiogram during surgery shows no definite pattern in our series. This is in accordance with the reports of other investigators.[22-28] However, in 12 of the 50 cases, there was a slowing of the pulse or lowering of blood pressure, or both, that was consistent with reflex vagal stimulation. These effects were sudden and transient, and had a direct relation to manipulation. These changes often could not be reproduced with the same stimuli in the same patient. This did not appear to be due to changes in depth of anesthesia, and often there was no further addition of thiopental or succinylcholine or changes in nitrous oxide concentration between repeated manipulations. The larger number of reflex changes in the electrocardiogram, blood pressure and pulse rate in the cardiac group is in agreement with the work of other investigators.[14,18,19,28,33,34] Five cases in the cardiac group demonstrated electrocardiographic changes concurrent with surgical manipulation of the biliary tract. The most severe was the appearance of atrioventricular dissociation during dissection in the region of the hilus of the gall blad-

der. The electrocardiogram of this patient continued to deteriorate, with ST-segment and T-wave changes along with intermittent runs of atrioventricular dissociation after the episode. Postoperatively, there was electrocardiographic evidence of a myocardial infarction. There was no significant change in pulse rate or blood pressure during surgery. One cannot be certain that the ensuing infarction was also related to the reflex that initiated the atrioventricular dissociation. Yet the appearance of tall, upright, symmetrical T waves, eventually taller than the QRS complex that followed within a few seconds of the end of the arrhythmia, suggests that the whole process was one and the same, and was related to coronary insufficiency that resulted in a myocardial infarction. The fact that, with this 1 exception, these reflex changes were never a threat to the patients in our series and did not require definitive treatment was due to their short duration and lack of severity. The appearance of potentially noxious reflexes during surgery in patients with previous cardiac disease may be the result of prolonged or intense stimuli or a lowered threshold in persons with unstable cardiovascular systems. This has been demonstrated in laboratory work,[34] and is occasionally observed clinically when mere palpation of the abdominal viscera gives rise to a severe vasovagal reflex with marked bradycardia and unobtainable blood pressure.

Gradual electrocardiographic changes not related to specific surgical manipulation were recorded in 70 per cent of the group with and 30 per cent of the group without cardiac disease. The electrocardiographic changes were similar in both groups — that is, ST-segment and T-wave variations were the most consistent finding. However, the patients without cardiac disease exhibited less severe and more transient changes, which did not persist in the immediate postoperative tracings. The patients with cardiac disease, on the other hand, had variations in the electrocardiogram that often persisted in the immediate postoperative tracings; 8 of this cardiac group showed significant improvement in the electrocardiogram during surgery, probably as a result of slowing of the pulse, lowered metabolism or the administration of higher concentrations of oxygen, and in 9 others the electrocardiographic abnormalities were more striking during surgery (in 6 of these, the deterioration persisted in the immediate postoperative tracing). Four of this group, as discussed above, later had electrocardiographic evidence of myocardial infarction. The precipitating factors of these infarctions were obscure and could only be re-

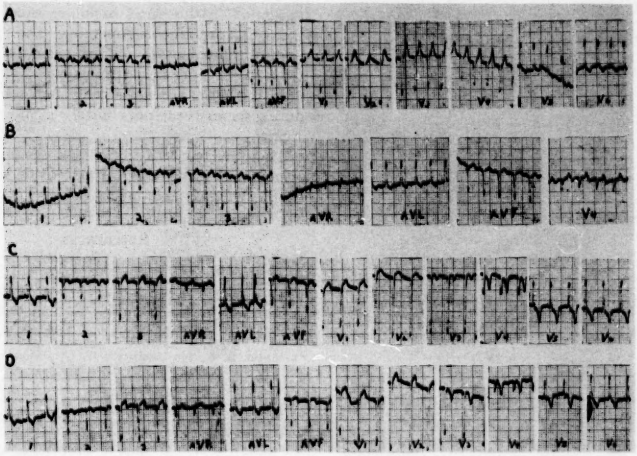

FIGURE 3. *Electrocardiograms in Case 36, a Sixty-six-Year-Old Man with a History of Myocardial Infarction (Paper Speed, 10 Mm. per Second).*

A = *preoperative electrocardiogram, showing complete left-bundle-branch block.*

B = *electrocardiogram taken immediately after operation, showing terminal inversion of the T wave in Lead* V_4.

C = *electrocardiogram taken on the ninth day, showing ST-segment depression in Leads 1, aVL and* V_4 *through* V_6 *(the T waves are deeply inverted in Leads 1, 2, aVL and* V_3 *through* V_6).

D = *electrocardiogram taken on the fourteenth postoperative day, showing a pattern similar to that observed in* C *(a follow-up tracing taken two months later was the same as the preoperative tracing).*

lated to specific surgical manipulation in the case mentioned above. None of the patients with electrocardiograms showing more marked abnormalities during surgery or postoperatively experienced bouts of hypotension, hemorrhage or hypoxia.

If reflexes that caused spasm or decreased coronary flow were involved they were not detectable by the means available. In 1 case in which infarction subsequently developed, transient reflex lowering of blood pressure and slowing of pulse occurred at a time when the T waves were already undergoing progressive changes to inversion. It appears that this myocardium, with electrocardiographic evidence of ischemia, would have been sensitized to any reflexes that decreased coronary flow. Yet in this case with obvious reflex blood-pressure and pulse changes, the simultaneously recorded electrocardiogram showed no transient deterioration during the period of the reflex. This does not rule out reflex vagal changes as being capable of causing decreased coronary flow. It may well be that the stimulus was neither prolonged nor intensive enough. It is more likely that the gradual ST-segment and T-wave changes in the absence of blood-pressure or pulse changes were from some cause that was not reflex. This may well have been some metabolic or chemical abnormality, as suggested by Raab.[38]

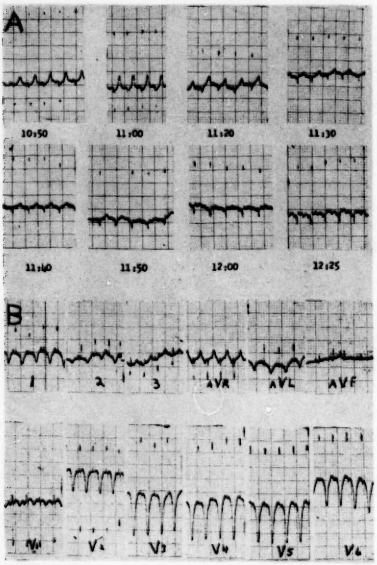

FIGURE 4. *Electrocardiograms in Case 46, a Seventy-five-Year-Old Woman with No History of Heart Disease and a Normal Preoperative Electrocardiogram (Paper Speed, 10 Mm. per Second).*

A *(Lead V_4), taken during surgery, shows the gradual onset of ST-segment elevation, together with progressive lowering of the T waves, terminating in inversion (note the increased depth of the Q waves).*

B, *electrocardiogram taken two days later, shows deeply inverted symmetrical T waves in Leads 1, 2, aVL and V_1 through V_6 (these changes persisted for six weeks).*

CONCLUSIONS

The frequency of "silent" postoperative myocardial infarction in this series of biliary-tract surgery suggests that routine preoperative and postoperative electrocardiograms should be taken on cardiac patients undergoing major surgery.

In this series reflexes arising from the biliary tract during surgery were not clinically significant except in 1 case.

There are few arrhythmias and conduction disturbances under thiopental, nitrous oxide and succinylcholine chloride anesthesia.

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USE OF PREDNISONE IN THE MANAGEMENT OF SOME HEMORRHAGIC STATES*

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PREVIOUS work has indicated the value of ACTH and cortisone in the management of thrombocytopenic purpura (idiopathic and secondary), anaphylactoid purpura, vascular pseudohemophilia and similar conditions.[1-13] The therapeutic efficacy of these drugs seems to depend on a complex series of specific as well as nonspecific effects.[14] Bleeding manifestations are strikingly decreased. For full therapeutic efficacy, however, doses of these hormones are required that often cause unpleasant side effects (such as salt retention, hypertension and potassium depletion).

The introduction of prednisone§ has supplied a corticosteroid hormone apparently free of some side effects of ACTH and cortisone. It was believed that this compound might be useful in the management of bleeding tendencies in which ACTH and cortisone have been previously employed with success.

MATERIAL AND METHODS

Six patients with idiopathic thrombocytopenic purpura, 4 with various types of acute leukemia, 2 with aplastic anemia, 3 with anaphylactoid purpura and 7 with vascular pseudohemophilia were the subjects of the study. Prednisone was administered orally in doses of 0.8 to 1.6 mg. per kilogram of body weight daily, depending on the severity of the bleeding manifestations. Patients were followed daily, with observations of their bleeding manifestations, routine blood counts, determination of bleeding time, tourniquet test and clot-retraction, prothrombin-utilization and thromboplastin-generation tests. The technics of these tests have recently been described.[15] Platelet counts were taken by a direct[16] as well as by an indirect[17] method, and their results checked by the observation of a well stained, well spread smear of peripheral blood. The results given in this paper are those obtained with the direct counting method. Platelet agglutinins were investigated by incubation of the patient's serum, inactivated and decalcified, with platelets of normal donors of Group O blood suspended in either their own plasma or saline solution. These technics have been described in detail.[18]

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§Kindly supplied as Meticorten by Schering Corporation, Bloomfield, New Jersey.

RESULTS

Idiopathic Thrombocytopenic Purpura

Four cases of the chronic and two cases of the acute variety of the disease were studied. Results of therapy varied considerably from case to case. There was a beneficial effect on the bleeding manifestations, and the tourniquet test became negative within forty-eight hours in all cases. The bleeding time was strikingly shortened within four to six days of treatment in all patients. The effect on the number of circulating platelets, however, varied from case to case from entirely negative result to striking rise in thrombocytes.

CASE 1. A.C., a 7-year-old boy, had severe cutaneous and mucosal bleeding 3 weeks after measles. At the time of the 1st examination, widespread petechiae were present, particularly over both legs and on the mucosa of the hard palate. The spleen was not palpable. Platelets were 17,000 per cubic millimeter, the tourniquet test was grossly positive (45 petechiae in an area 1 cm. in diameter after application of median pressure for 5 minutes), the bleeding time was 16 minutes, and clot retraction was 12 per cent; prothrombin activity of the plasma was 82, and that of the serum 75 per cent. Bone-marrow examination revealed moderate erythroid hyperplasia and increased number and immaturity of megakaryocytes, which showed poor granularity of the cytoplasm and were not surrounded by platelets. Platelet agglutinins were not detected in the patient's serum.

The patient received 50 mg. of prednisone daily for 28

days, after which the drug was reduced progressively and then discontinued. No new hemorrhagic manifestations were noted after the 3d day, when the tourniquet test became negative. The bleeding time was also shortened to 9 minutes on the 4th day of therapy. The platelet count rose slowly, but failed to reach normal values. On suspension of therapy, the platelet level fell slowly, and the bleeding time became progressively longer. There was, however, no return of purpura or positivity of the tourniquet test until 12 days after suspension of therapy. Two months later, the platelet count began to rise spontaneously, and the patient made an uneventful recovery. This case

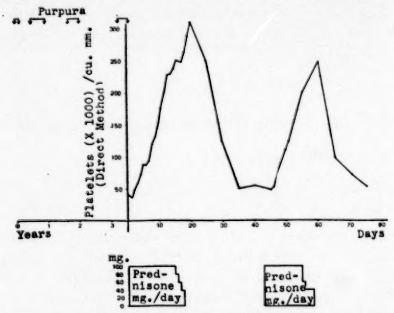

FIGURE 1. *Effect of Prednisone Therapy in a Forty-three-Year-Old Woman with Chronic Idiopathic Thrombocytopenic Purpura.*

was considered to represent a failure of prednisone therapy in a patient with the acute, self-limited type of the disease.

The administration of prednisone may have accelerated spontaneous recovery in the other case of acute idiopathic thrombocytopenic purpura:

CASE 2. In B. J., a 4-year-old girl, severe epistaxis and cutaneous bleeding developed 2 weeks before examination. There was no history of exposure to drugs or infection. Two transfusions of platelet-rich normal plasma[14] were administered within 18 hours of admission for the relief of nasal, gastrointestinal and cutaneous bleeding. The platelet count was 10,000 per cubic millimeter, and all other laboratory tests gave results typical of severe thrombocytopenia. A bone-marrow preparation showed a normal number of megakaryocytes, most of them, however, exhibiting degenerative changes of the nucleus and vacuolization of the cytoplasm. Search for platelet agglutinins was again negative. Prednisone was started at a dose of 40 mg. daily. Clinical signs of bleeding disappeared 2 days after initiation of therapy; the tourniquet test became negative within 48 hours, and the bleeding time was shortened from 28 to 12 minutes in 72 hours. The platelet count began to rise on the 5th day of therapy and was found to be 325,000 on the 10th day. Remission was sustained over a period of 4 months. Owing to the well known unpredictability of course in idiopathic thrombocytopenic purpura it is extremely difficult to determine whether the prompt remission was caused, accelerated by or only coincidental with the administration of prednisone.

Effects of prednisone on the chronic variety of the disease were also variable. In 1 case sustained remission was obtained as long as the administration of the drug was continued:

CASE 3. P.R., a 43-year-old woman, was admitted to the hospital with a 3½-year history of profuse and lengthy menstrual periods and occasional episodes of mucosal and cutaneous bleeding, lasting at times for several months. At the 1st examination the platelet count was 40,000 per cubic millimeter. Bone-marrow aspiration showed an increased number of megakaryocytes, mostly of mature type, surrounded by few platelets, with poor granularity of the cytoplasm. Search for platelet agglutinins was negative, as was an L.E. test. On administration of 100 mg. of prednisone daily, the platelet count rose rapidly, only to fall promptly on discontinuation of therapy (Fig. 1). The intermittent use of the drug, however, has since proved of value in controlling the clinical bleeding that occurs from time to time.

Perhaps the most gratifying therapeutic result has been obtained in the management of a case of chronic idiopathic thrombocytopenic purpura with detectable platelet agglutinins:

CASE 4. R.W., a 37-year-old woman, had a history dating back 4 years before admission when she had an episode of severe mucosal and cutaneous bleeding. Intracerebral bleeding may also have occurred at that time. Hemorrhagic manifestations subsided slowly, but, since that time, she had noted severe and prolonged menstrual periods and occasional crises of cutaneous and mucosal bleeding, and the platelet count had been found to be persistently low. On examination nasal and gingival bleeding and diffuse petechiae were present. The platelets were 35,000 per cubic millimeter, and all hemorrhagic tests reflected the state of thrombocytopenia. An L.E. test was negative. Bone-marrow aspiration showed an increased number of megakaryocytes, mostly of the mature type, with marked lack of cytoplasmic granularity. Platelet agglutinins were present in the patient's serum at a titer of 1:128. On administration of 100 mg. of prednisone a day the platelet count rose rapidly and, 25 days later, had reached normal values (Fig. 2). Bone marrow aspirated at this time showed normal megakaryo-

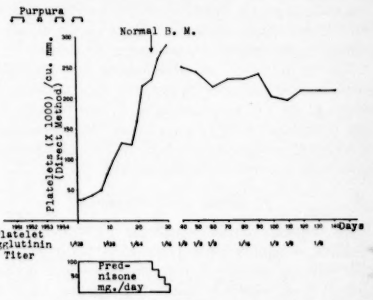

FIGURE 2. *Effect of Prednisone Therapy in a Thirty-seven-Year-Old Woman with Chronic Thrombocytopenic Purpura of Presumably Idiopathic Nature.*

cytes, and the titer of platelet agglutinins was lowered to 1:16. The drug was reduced progressively and then discontinued. The platelet count, however, has been normal since, and the titer of platelet agglutinin has remained at a level of 1:8. Clinical and hematologic remission had lasted for 4 months when the patient was last seen.

In the 2 remaining cases the platelet count was entirely unaffected by the use of prednisone, although there was striking improvement in the bleeding manifestations.

CASE 5. L.W.R., a 44-year-old woman, had suffered from intermittent bouts of cutaneous and mucosal bleeding since

1938. The platelet count had been uniformly low at all times, reaching values of 20,000 per cubic millimeter in periods of very severe bleeding. At 1 time ovarian irradiation was resorted to for the control of profuse menstrual bleeding. Menstrual flow was then interrupted for 10 months. Splenectomy was carried out in 1949, with fleeting clinical remission, but without elevation of the platelet count. At the time of examination the platelet count was 14,000 per cubic millimeter, and the few thrombocytes seen were large and bizarre. Megakaryocytes were abundant in the bone marrow, and showed karyorrhexis and lack of cytoplasmic granularity. A search for platelet agglutinins was negative. The patient received 100 mg. of prednisone daily for 30 days. Although there was no significant elevation of the platelet count (Fig. 3) bleeding manifestations were temporarily reduced in severity, capillary resistance (tourniquet test) improved, and the bleeding time was shortened. The drug was then gradually reduced in dosage and finally discontinued. After 3 weeks of rest, 400 mg. of cortisone was given daily for 25 days, also without result. ACTH was administered 1 month later in a dose of 200 units daily for 20 days. The platelet count rose to 150,000 per cubic millimeter within 1 week, and there was prompt regression of bleeding manifestations and a return to normal of hemostatic function. Suspension of therapy, however, was followed by drop in the platelet count within 6 days.

Improvement of bleeding manifestations without elevation of the platelet count was also obtained in another patient with chronic idiopathic thrombocytopenic purpura in whom splenectomy had not yet been performed. This has been recently carried out, and, four weeks after the operation, the platelet count was still low, although there had been improvement in the severity of the bleeding manifestations.

Thrombocytopenia of Acute Leukemia

Prednisone was used in 4 cases of acute leukemia, primarily for the prevention and control of bleeding manifestations in the course of therapy with chemotherapeutic agents. The effect of the drug was compared with that obtained in similar cases with the oral use of comparable doses of cortisone. This series included 1 child with acute lymphocytic leukemia treated with 4-amino-N^{10} methylpteroyl glutamic acid (Methotrexate), 2 cases of acute histiocytic leukemia treated with 6-mercaptopurin and 1 case of acute myelogenous leukemia treated with Myleran and, after three weeks of unsuccessful therapy, with 6-mercaptopurin also. Doses of 1.5 mg. per kilogram of body weight daily were consistently employed. The effects were similar to those observed with comparable doses of cortisone: a sense of well-being and temporary reduction or suppression of bleeding manifestations. In no case of this obviously small series was the use of prednisone at the doses employed believed to have favored the control of the leukemic disease.

Thrombocytopenia of Aplastic Anemia

Two patients with aplastic anemia were given doses of 1.5 mg. of prednisone per kilogram of body weight for twenty weeks. One case was entirely idiopathic; the other, in a truck driver, might have been related to prolonged exposure to gasoline fumes. The only important effects observed were reduction in the bleeding manifestations, a return to normal of the tourniquet test, some shortening of the bleeding time and, in 1 case, a fleeting elevation of the platelet count. There was no reduction in the requirement for blood transfusions.

Anaphylactoid Purpura

Two cases of the acute variety and 1 of the chronic variety of the disease were treated.

The 1st patient, a 5-year-old boy, had no past history of the disease. He was admitted to the hospital because of melena with crampy abdominal pains, followed within 2

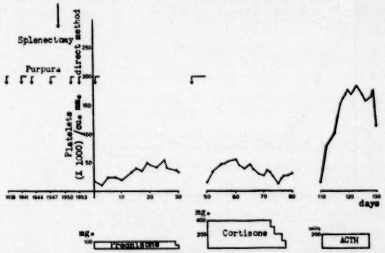

FIGURE 3. *Comparative Effect of Prednisone, Cortisone and ACTH on the Platelet Count in a Forty-four-Year-Old Woman with Chronic Idiopathic Thrombocytopenic Purpura after Splenectomy.*

days by a skin rash limited to the legs and buttocks and consisting of the typical large, confluent deep-purplish hemorrhagic macules. Examination of the urine was negative. Prednisone was given in a dose of 20 mg. daily for 10 days. Pain and melena disappeared within 2 days, and the skin lesions faded within 6 days. Because of, or in coincidence with, the administration of the drug, there has been no relapse of the disease for the past 6 months, although the patient has suffered repeatedly from colds. Punch skin biopsy, taken before and 10 days after therapy, showed changes identical to those previously described in 1 patient treated with ACTH.[13]

The 2d patient, a 42-year-old woman, had a typical rash all over the body except for the face and trunk, hematuria and joint pains, possibly related to allergy to penicillin. The nonprotein nitrogen was 59 mg. per 100 ml. She received 70 mg. of prednisone daily for 10 days. All symptoms regressed in about 1 week. The skin lesions reappeared 5 days after discontinuation of therapy and were again promptly remitted on its reinstitution. Two months later the urine had cleared completely, and the nonprotein nitrogen serum was 29 mg. per 100 ml.

Also treated was a 45-year-old man with the chronic variety of the disease of 2 years' duration. There was a typical skin rash gradually ascending from the feet to the waist, made worse by standing and improved by bed rest, but no articular, intestinal or renal manifestations. An L.E. test was negative. A skin biopsy showed focal smudging of collagen bundles in the skin and underlying stroma, a pericapillary infiltrate with many polynucleates, a few lymphocytes and tiny hemorrhages of the dermal papillae. The epidermal appendages appeared to be involved in the inflammation. The focal areas of inflammation extended into the underlying subcutaneous fat, being most marked in the superficial dermis. These findings were clearly consistent with anaphylactoid purpura. The patient received 50 mg. of prednisone daily for 20 days without any improvement of the cutaneous lesions by either appearance or repeated skin-biopsy findings. The only effect observed was a decrease of blood sedimentation rate from 62 to 28 mm.

in 1 hour (Westergren method). This value returned to the original level 2 weeks after suspension of therapy. The patient later improved with management of the pulmonary disease (postural drainage, inhalation therapy and so forth).

Vascular Pseudohemophilia

The definition of pseudohemophilia applies to all hemorrhagic diatheses in which a prolonged bleeding time is the characteristic finding. We like to distinguish between a vascular and a platelet-deficiency type of this syndrome, the first being due to a con-

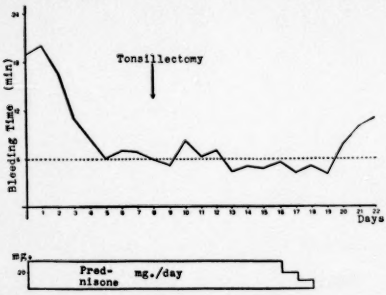

FIGURE 4. *Effect of Prednisone on the Bleeding Time in a Seven-Year-Old Boy with Vascular Pseudohemophilia.*

genital abnormality of the vascular tree, and the second to qualitative platelet deficiency. Prednisone was used in the management of 7 cases of vascular pseudohemophilia as defined here. Doses of 0.5 to 1 mg. per kilogram of body weight were given daily. All patients had typical findings of the disease, including normal platelet number, normal clot retraction and negative tourniquet test. In all cases, isolated patients' platelets corrected the deficient clot retraction and prothrombin consumption of normal platelet-free native plasma. Typical behavior of the bleeding time during therapy is shown in Figure 4. The bleeding time was reduced from nineteen to seven minutes within six days and then to five minutes within two weeks. Two of these patients were successfully operated on for tonsillectomy after treatment for four to seven days, the drug being continued for eight days after surgery and then slowly discontinued.

Complications of Therapy

Two of the 23 patients treated had a past history of peptic ulcer, but no exacerbation was noted during prednisone therapy. Edema was not noted in any of the patients although there was no limitation of sodium chloride intake. In 3 of the 23 cases there was a modest fall in the level of serum potassium, which was prevented by oral supplements of 250 to 1000 mg. of potassium chloride daily. In 2 of these cases intermittent muscular cramps and crampy abdominal pains and in 1 marked pigmentation of the face, trunk and arms developed. Another patient manifested a butterflylike rash over the face on suspension of therapy that lasted for four weeks and then scaled and disappeared. In 1 case severe insomnia, resistant to all narcotics and barbiturates, occurred but disappeared on suspension of therapy and did not reappear when ACTH was administered. Levels of ascorbic acid in the plasma were determined at frequent intervals in 16 patients, because of our experience with ACTH and cortisone.[19] In 8 of 23 patients a drop in ascorbic acid level was noted from 0.8 to 1 mg. per 100 ml. to 0.4 to 0.6 mg. These levels returned to normal within two days of administration of 300 mg. of ascorbic acid daily. No thromboembolic complications, hypertension or glycosuria was noted in this series.

Discussion

The use of ACTH or steroid hormones (cortisone and hydrocortisone) has become standard procedure in the treatment of thrombocytopenic states. Their main indications, as previously outlined,[14] include various phases of idiopathic thrombocytopenic purpura, secondary thrombocytopenia of leukemic disease or aplastic anemia, pseudohemophilia (vascular type) and anaphylactoid purpura. In our experience, similar indications seem to exist for prednisone.

Our series is obviously too small to permit definite conclusions. Those presented here are preliminary, particularly so far as the activity of prednisone as compared with that of ACTH and cortisone is concerned. Although of significant value, prednisone seeems less effective than cortisone or ACTH in the management of idiopathic thrombocytopenic purpura and in the control of thrombocytopenic bleeding of leukemia and aplastic anemia, irrespective of dose. It is, on the other hand, particularly valuable in vascular pseudohemophilia and in acute anaphylactoid purpura. The low doses needed to reduce the bleeding manifestations in pseudohemophilia and in acute anaphylactoid purpura appear to make this drug the agent of choice in the management of these disorders.

Another stated advantage of prednisone is the avoidance of side effects of medication. In this series prolonged therapy with high doses was not accompanied by development of edema or hypertension. Thus, the drug may have useful application, when it may be desired to reduce such side effects. As can be seen from the description of many other complicating features encountered, however, the use of the drug is not entirely without risk at such high dosage. As with ACTH and cortisone, careful supervision of the patient remains necessary and desirable.

Summary

Prednisone was used in doses of 0.8 to 1.6 mg. per kilogram of body weight to control the bleeding mani-

festations of idiopathic and secondary thrombocytopenia, vascular pseudohemophilia and anaphylactoid purpura. The drug was found to be of special value in the management of vascular pseudohemophilia and acute anaphylactoid purpura. Multiple complications suggested the necessity of careful supervision of the patient during treatment.

Since this paper was submitted for publication 3 additional cases of chronic idiopathic thrombocytopenic purpura, 2 cases of thrombocytopenia of acute leukemia, 2 cases of thrombocytopenia of aplastic anemia and 1 case of anaphylactoid purpura have been treated with prednisone. Results obtained are entirely comparable to those reported in the article. Among these 8 patients, peptic ulcer developed in 1 after the administration of 12 gm. of the drug. Another showed marked pigmentation of the body, involving primarily the trunk, face and arms and sparing the abdomen entirely. Ascorbic acid deficiency was noted in 2 additional patients in this series.

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POSTABORTAL *CLOSTRIDIUM WELCHII* SEPSIS WITH MASSIVE HEMOLYSIS*

Report of a Case

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NEW HAVEN, CONNECTICUT

CLOSTRIDIUM welchii sepsis is one of the most serious complications of induced abortion. The majority of these patients are admitted on obstetric services, and most of the reviews of this subject have appeared in the obstetric literature. However, the manifestations of generalized sepsis are often so pronounced that the nature of the underlying process is obscure. Recently, a patient of this type was admitted to the University Medical Service of the Grace–New Haven Community Hospital with a tentative diagnosis of acute hemolytic anemia of undetermined cause. The associated diagnostic and therapeutic problems seem of sufficient general medical importance to warrant our reporting this case and discussing the clinical syndrome.

Case Report

R. J. (G.–N.H.H. 428965), a 28-year-old divorced Negress, was admitted to the Grace–New Haven Hospital on June 12, 1955. Two days previously vaginal bleeding, considerably more profuse than her usual menstrual period and about 1 week before her expected menstrual date, occurred. Several hours later she experienced severe epigastric pain, which rapidly became generalized and was associated with nausea, vomiting and diarrhea. During the next 2 days the abdominal pain persisted, and she passed 10 to 15 watery stools per day. During the day before admission she had several shaking chills, felt feverish and was told that her scleras appeared brown. On the day of admission she noted a mild sore throat, frontal headache and severe generalized muscular aching. The urine volume had been scanty since the onset of her illness.

A normal menstrual period was recorded on May 19, and last coitus had occurred 2 months prior to admission. The patient denied, in a most convincing manner, that any attempt at abortion had been made, and gave no history of either drug ingestion or exposure to toxic agents. The past history was significant only in that she had had 3 normal pregnancies, and 4 years previously a dilatation and curettage had been performed for hydatidiform mole.

Physical examination disclosed a moderately obese, somewhat dehydrated and acutely ill woman. There was striking bilateral brownish discoloration of the scleras. The heart and lungs were not remarkable. The abdomen showed diffuse, exquisite tenderness to palpation, with rebound pain but little or no involuntary muscle spasm. The bowel sounds were diminished, but present. Blood was present in the vagina, and a small amount of necrotic tissue protruded from the cervical os. The uterus was tender, and its size

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was consistent with a pregnancy of 6 to 8 weeks. Impressive generalized muscular tenderness was observed.

The temperature was 101°F. by rectum, the pulse 140, and the respirations 20. The blood pressure was 120/80.

Approximately 20 ml. of dark-brown, guaiac-positive urine was obtained on admission. It gave a negative test for bile and a ++++ test for albumin, with 13-15 erythrocytes and 50-75 leukocytes per high-power field in the sediment. Hematologic studies showed a hematocrit of 26 per cent and a total leukocyte count of 65,000, with 54 per cent segmented cells, 39 per cent band forms and 7 per cent lymphocytes. An occasional nucleated erythrocyte, moderate microspherocytosis and moderate platelet diminution were noted. The reticulocyte count was 2 per cent. The cold-agglutinin, sickle-cell, L.E. and Coombs antiglobulin tests were negative. A sternal-bone-marrow aspiration demonstrated a moderate degree of erythroid hyperplasia. The marrow was very cellular and contained a normal amount of hemosiderin. A buffy-coat smear of a heparinized blood sample that had been incubated for 15 minutes at room temperature revealed the presence of many phagocytized erythrocytes. From 1 to several erythrocytes in various stages of preservation were found in the cytoplasm of about 20 per cent of all monocytes present. The plasma was the color of port-wine and spectroscopic examination showed that both methemalbumin and oxyhemoglobin were present. Osmotic fragility was increased significantly (Fig. 1).

About 5 ml. of brown, cloudy fluid was obtained by colpopuncture. It contained many pus cells, and culture revealed *Proteus vulgaris, Streptococcus faecalis* and *Cl. welchii*. Blood culture was positive for *Str. faecalis*, which was sensitive to both penicillin and the tetracycline group of antibiotics. A cervical culture grew out *P. vulgaris, Str. faecalis* and *Cl. welchii*. A culture of the urine contained both *P. vulgaris* and *Cl. welchii*, whereas one of the stool showed only *P. vulgaris* and *Escherichia coli*. The nose and throat cultures showed only the normal upper respiratory flora. The clostridium obtained from the urine was injected into the thigh of a mouse. It produced an inflammatory reaction with emphysema in the muscle.

The patient's serum was added to a crude lecithovitellin preparation in an attempt to demonstrate the presence of alpha toxin, but no evidence of hydrolysis was observed. Serologic tests for *Salmonella typhosa* and *S. paratyphi A* and *B* were negative. A stool specimen gave a positive guaiac reaction.

The initial blood chemical studies showed the nonprotein nitrogen to be 71 mg., the sugar 44 mg., the albumin 2.78 gm., and the globulin 2.36 gm. per 100 ml.; the carbon dioxide was 14.6 milliequiv., the chloride 90.2 milliequiv., the sodium 132.9 milliequiv., and the potassium 5.3 milliequiv. per liter. The serum amylase was 175 units, and the uric acid 8.6 mg. per 100 ml. Liver-function studies indicated a total bilirubin of 10.3 mg. per 100 ml. (9.6 mg. per 100 ml. indirect acting), negative cephalin flocculation, a thymol turbidity of 7.8 units and an alkaline phosphatase of 5.3 Bodansky units. The subsequent pertinent changes in blood chemical values are shown in Table 1.

X-ray examination of the chest revealed nothing remarkable, but films of the abdomen showed poor psoas shadows and a suggestion of free peritoneal fluid. An electrocardiogram revealed sinus tachycardia and right-axis deviation.

Two hours after admission the hematocrit had fallen from 26 to 19 per cent. Parenteral fluid therapy was started, and 1 hour later the hematocrit was 15 per cent; 1500 ml. of blood was given, with a rise in the hematocrit to 23 per cent, where it remained throughout the hospital course. The patient was given 900,000 units of aqueous penicillin, 800,000 units of procaine penicillin and 1 gm. of streptomycin per day. By the 2d day she had become afebrile, the pulse had slowed to about 80, and the blood pressure was maintained at about 140/90. The diarrhea stopped, but myalgia and abdominal pain persisted. On the 3d hospital day a currettement of the uterus was performed. A large

TABLE 1. *Blood Chemical Values during the Hospital Course.*

Hospital Day	Nonprotein Nitrogen	Carbon Dioxide	Chloride	Sodium	Potassium	Bilirubin (Total)
	mg./100 ml.	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*mg./100 ml.*
1	71	14.6	90.2	132.9	—	10.3
2	105	15.3	90.5	133.8	5.3	—
3	151	15.7	94.5	130.0	6.1	40.7
4	191	16.2	84.0	131.3	5.3	37.0
5	230	14.5	89.0	127.5	4.6	12.9
6	286	13.7	87.2	130.7	5.3	5.9
7	311	12.9	88.5	125.0	5.5	—
8	334	11.0	90.7	127.5	7.6	—
9	348	10.1	87.0	136.0	7.7	3.3

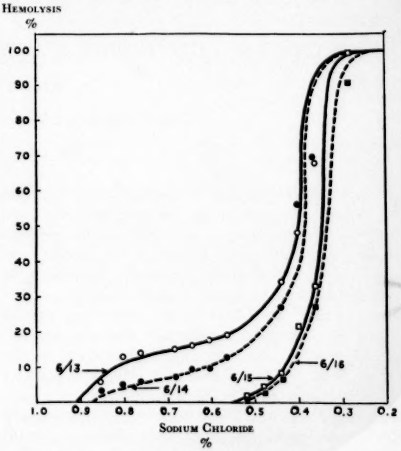

FIGURE 1. *Osmotic Fragility in a Patient with* Cl. welchii *Sepsis.*

It should be noted that the first osmotic-fragility determination (6-13) was performed on the day after a transfusion of 1500 ml. of whole blood.

amount of foul, bloody, necrotic material was removed, and a small amount of gas was observed bubbling from the cervical os. Histologic examination of this material showed it to be decidua. The streptomycin was discontinued because of the persistence of anuria, but the procaine penicillin was continued in a dosage of 2,400,000 units per day. On the 4th day she was given 8 vials of gas-gangrene antitoxin.

During the next several days she remained alert and comfortable. Abdominal and muscle pains disappeared, but the anuria persisted. The serum gradually changed to a light yellow color. The leukocyte count stayed around 30,000. The reticulocyte count remained between 1.5 and 2.0 per cent. Fluid intake was kept between 600 and 900 ml. of 20 per cent dextrose in water per day. Digitalis was given to offset the adverse cardiac effects of the elevated serum potassium. The weight remained constant, and edema did not develop. Because of a low serum calcium, calcium gluconate was added to many of the infusions.

In spite of this regimen, on the 8th hospital day the serum potassium rose to 7.6 milliequiv. per liter, and the patient appeared somewhat more lethargic. On the following day, without any great change in the serum potassium level, she became comatose, and a nodal rhythm, with moderately peaked T waves, appeared in the electrocardiogram. An attempt was made to lower the serum potassium level with a cation-exchange resin given by rectum, but without success, and she died on that day.

Autopsy revealed an acute necrotizing parametritis and bilateral pulmonary congestion, with pleural effusion and ascites. In addition there was congestion of the liver, spleen and kidneys, severe swelling of the kidneys and generalized icterus. Post-mortem cultures from the endometrium were positive for *Cl. welchii*.

Discussion

The clinical aspects of postabortal and puerperal clostridia infections have been well described.[1] The case presented above was not particularly different from many cases recorded in the literature. The picture may vary from a mild illness to a fulminating septicemia, with evidence of massive intravascular hemolysis, which is often seen in the postabortal cases. There is usually a history of mechanical interference with pregnancy. Although the patient described above vehemently denied any such interference it is likely that the abortion was induced; however, it is conceivable that the infection developed after spontaneous abortion. *Cl. welchii* in significant numbers have been recovered from vaginal cultures of normal pregnant women.[2]

The initial symptoms frequently consist of nausea, vomiting and abdominal and general muscle pain. Diarrhea, though somewhat less common, is not an unusual presenting complaint. Many authors have emphasized the alertness and relative well-being of the patient in spite of the gravity of the illness. On the other hand, cyanosis and circulatory failure may supervene, and the process may be so rapid as to cause death within a few hours. The fever is often of low degree and is an unreliable index of either the severity of the illness or the response to therapy. The pulse usually is disproportionately rapid; the systolic, diastolic and pulse pressures tend to be low. The pulse and blood pressure are better criteria of prognosis than fever. The physical findings may be few at the onset, the most striking being dehydration, generalized moderate to severe muscle tenderness and obvious icterus. Pelvic examination should be consistent with the duration of pregnancy.

The laboratory findings are characteristic of an acute bacterial infection with intravascular hemolysis. The leukocyte count is invariably elevated, with a shift to the left in the granulocytic series. Varying degrees of thrombocytopenia[3] and anemia occur.

Hemolysis may be mild, with only slight elevation of the serum bilirubin, but it is frequently severe, free heme pigments being present in the plasma and urine — in such cases lower-nephron nephrosis, with the usual alterations in blood chemical findings, frequently develops.

For the first two days in the hospital the precise etiology of this patient's illness was not apparent, but was suspected. The clinical picture in many ways was characteristic; however, the possibilities of either rupture in ectopic pregnancy or drug toxicity existed. The low degree of fever combined with the general well-being of the patient made us suspicious of some illness other than an overwhelming septicemia. The negative colpopuncture and eventual isolation of *Cl. welchii* from numerous sites on the third hospital day made the etiology of the illness clear.

In the majority of these cases there is a mixed uterine infection, and it is not surprising that in this case *Str. faecalis* was cultured from the blood. Also, it is not a unique experience to fail, as we did, to demonstrate clostridia in the blood culture. The organism does not survive for long periods in the blood, and signs of toxemia may be present in the face of a negative culture.[4] Since it is known that active alpha toxin may enter the circulation from a local infection,[3] it also seems possible that this hemolysin was absorbed from the uterus and that bacteremia had not occurred.

Alpha toxin, a lecithinase, is the hemolytic exotoxin produced by *Cl. welchii*. An attempt to demonstrate the presence of alpha toxin in the serum of this patient by its hydrolyzing action on lecithovitellin was not successful. It should be pointed out that although the serum used was obtained when the patient was first seen, it was not tested until after it had been stored in a freezer for a few days. However, it seems unlikely that even fresh serum would have given positive results. Furr et al.[3] attempted to demonstrate alpha toxin in the serum of dogs after giving it by infusion. Only after very large amounts (100 M.L.D. per kilogram of body weight or more) had been administered could traces of this material be detected.

The treatment of this patient was chiefly a problem in the management of renal failure. The infection seemed to be controlled adequately with penicillin, and there was no evidence that hemolysis had continued after the first hospital day. The efficacy of gas-gangrene antiserum is unsettled. The average daily fluid intake was 600 ml., excluding the day of

admission, when it was considered desirable to give more vigorous hydration. On this program there was no weight gain, and she remained in satisfactory water and electrolyte balance despite the progressive azotemia and persistent anuria. On the last hospital day her condition deteriorated rapidly although there was only a moderate elevation of the serum potassium. Attempts were made to arrange for extrarenal dialysis, but were unsuccessful. It remains subject to speculation whether or not this procedure would have altered the final outcome.[5]

Certain hematologic features of this case deserve particular emphasis. The massive intravascular hemolysis was made apparent by the profound and rapidly progressing anemia, along with the presence of free hemoglobin and methemalbumin in the plasma. The positive identification of these heme pigments was substantiated by spectroscopic and chemical methods. The absorption bands of oxyhemoglobin were visible upon appropriate dilution of the plasma with saline solution. However, the absorption band in the red portion of the visible spectrum could have been either methemoglobin, as has been reported previously,[1] or methemalbumin. Failure to demonstrate the presence of methemoglobin in the erythrocytes and the use of differential reactions in the plasma (that is, 5 per cent potassium cyanide and 5 per cent hydrogen peroxide) indicated that methemalbumin rather than methemoglobin was the pigment present. This heme protein undoubtedly was responsible for the brown color of the plasma.

The presence of microspherocytes in the peripheral blood has been emphasized by others.[6] In the case reported above, they were moderately prominent, but the presence of damaged or altered cells was demonstrated better by the osmotic-fragility and plasma-incubation studies. On the day after the initiation of antibiotic and transfusion therapy a large portion of the circulating red-cell population was abnormally sensitive to hypotonic saline solution. This was less marked on the following day, and within two days osmotic fragility had returned almost entirely to normal. After the first hospital day there was no further clinical evidence of increased erythrocyte destruction. The extensive erythrophagocytosis observed on stained buffy-coat films of the incubated plasma from the patient again demonstrates the presence of damaged, coated or altered cells. This in vitro phenomenon probably represents the in vivo removal mechanism by reticuloendothelial tissue for a great many of the erythrocytes injured by the alpha toxin of the *Cl. welchii*. It is of considerable interest that extensive erythrophagocytosis has been observed in the bone marrow of dogs after an infusion of alpha toxin.[3]

In spite of the episode of massive hemolysis the patient subsequently did not have an impressive reticulocytosis, nor did the hematocrit level improve. The lack of expected erythropoietic response was probably due to the progressive azotemia and smoldering infection. Furthermore, the number of erythroid precursors in the marrow was increased only moderately. Some of the lack of more extensive marrow erythroid hyperplasia was undoubtedly due to the azotemia and infection but also to the relative increase in myeloid elements in response to the infection. Additional transfusions were not given for fear that another hemolytic episode might further impair renal function and increase the plasma potassium concentration. There was also the possibility of inducing cardiac failure through too rapid expansion of the blood volume. In retrospect, however, it might have been wise to have supplemented the circulating hemoglobin level with a few additional transfusions.

The ability of clostridial organisms of the gas-gangrene group to produce severe intravascular hemolysis makes their position unique in this respect. Many other bacteria have been designated as having a similar role, but reliable documentation has been lacking.

Summary

A fatal case of postabortal septic endometritis with massive hemolysis is presented.

The significance of hemoglobinemia, methemalbuminemia, erythrophagocytosis and increased osmotic fragility in this disorder is emphasized.

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MEDICAL PROGRESS

DISEASES OF MUSCLE

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PERIODIC paralysis and Thomsen's disease (myotonia congenita) have been placed under a new division of muscle disease, "Disorders of Excitability and Contractility."[1] In the 1951 Medical Progress report on primary diseases of muscle, periodic paralysis was not included.[2]

The report of the third Progressive Muscular Dystrophy Conference is now in print.[3] There were four scientific symposiums, the first under the chairmanship of Wallace O. Fenn, Ph.D., being entitled "Recent Advances in Basic Muscle Chemistry, Physiology and Pharmacology," the second, under the chairmanship of Ralph W. Gerard, Ph.D., M.D., D.Sc., being entitled "Recent Advances in Knowledge of Metabolic Alterations in Muscular Dystrophy," the third, under the chairmanship of Herbert S. Gasser, M.D., being entitled "Contracture of Muscle," and the fourth under the chairmanship of Derek E. Denny-Brown, M.D., being entitled "Regeneration and Growth of Muscle."

Dr. Fenn, in his introduction, makes the following comment:

> We may consider the contractile machinery itself as a possible cause of the deficiency of muscular dystrophy. Here we have the still unproved suggestion of Zierler, that because of some metabolic defect it may be impossible to synthesize proper quantities or qualities of actomysin. My friend, Dr. Mason, would tell me there is evidence in the histological picture because the muscle doesn't "look right" under the microscope.
>
> There may be some less obvious chemical defects in the contractile machinery in dystrophic muscles. It was shown long ago that the concentrations of K and Mg are low while those of Ca and Na are high. It may be true that each individual fiber contained abnormally high concentrations of Na and abnormally low concentration of K as in a fatigued muscle. Rats raised on a low K diet, according to Cannon, developed heart lesions not unlike those seen in muscular dystrophy, but only when there is a high concentration of Na in the diet.
>
> It may be that the contractile machinery is in good order but the power supply is absent. The mechanism whereby the A.T.P. is broken down into A.D.P. may be defective.

In his introduction, Dr. Gerard characterizes the cells in muscular dystrophy as follows:

> It does look very much as if these muscle cells, cultured and subcultured for some two months by now, remain distinctly abnormal as individual cells in culture, or at least, distinctly different from muscle fibers of normal individuals cultured under the same conditions. The dystrophy cells show amitotic division; they never show contraction, which the normal ones do quite regularly; and, perhaps most striking, they show no cross-striation, which the normal ones exhibit.

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PROGRESSIVE MUSCULAR DYSTROPHY

The late distal form of muscular dystrophy is reported by Welander,[4] from Sweden, who examined 249 patients. The onset was usually between forty and sixty years of age, and 149 were men. The disorder is inherited as a mendelian dominant. The extensor muscles of the fingers are the first affected, and later the extensors of the hands, toes and feet. The span of life is not shortened, and the slow progress of the disease does not lead to complete incapacity. There is a rare homozygous type inherited from both parents. Weakness starts in the distal muscles of the legs, and the patient is completely incapacitated in ten to fifteen years.

At autopsy and biopsy the nervous system was normal in 3 and showed primary myopathic changes in 27 cases.

Stephens and Tyler[5] make plain the difficulty in studying human heredity when a recessive trait is involved. Childhood progressive muscular dystrophy is described in 63 patients in 33 separate kindreds, in 14 of which there were insufficient data to draw conclusions regarding inheritance, whereas in 12 kindreds there was definite evidence that sex-linked recessive traits represented new mutations. Only in 7 kindreds was there proof of sex-linked recessive inheritance.

The high mutation rate in muscular dystrophy and the failure of patients to reproduce account for the frequently sporadic occurrence of the disorder.

Familial Ocular Myopathy

One patient with familial ocular myopathy[6] (a sixty-eight-year-old man) died of a myocardial infarct. Ptosis had been progressive from the age of twenty; he also had weakness of the eye muscles that later became progressive. At autopsy the nuclei in the midbrain were normal; there were dystrophic lesions of the eye muscles, and the other muscles were not affected. His two sons, fifty-four and forty-nine years of age, had ptosis that began in their teens. Subsequently, the eye muscles were affected. It was questionable whether the son of one was affected. The son of the other had questionable, mild ptosis.

The authors state that a survey of the literature on external ophthalmoplegia shows that in an article in *Brain* in 1928, Landon and Cadwalader had not examined the eye muscles of the patients and had called the lesion nuclear. The type of heredity was ques-

tionably dominant sex linked but could also be recessive. Incompletely sex-linked muscular dystrophy can be recessive, sex linked or not, dominant and of low or high penetrance.

Writing on the heart in muscular dystrophy, Weisenfeld and Messinger[7] reported an autopsy that showed, in the posterior aspect of the left ventricle, myocardial fibers that were small and fragmented, each vessel being surrounded by dense, atrophied connective tissue.

In a group of 44 patients with muscular dystrophy 85 per cent had signs of dysfunction of the cardiovascular system. In 80 per cent abnormalities of the electrocardiogram were observed. Six autopsies are reported.

Lightwood[8] writes on the bone and joint abnormalities in childhood muscular dystrophy. He describes 2 small boys with dystrophy and limitation of extension of the knees. Walton and Warrick[9] consider the changes in the bones secondary to lack of normal stresses and strains.

Tyler and Perkoff[10] ask the question, "Is muscular dystrophy endocrine or metabolic?" They ran 28 patients with progressive muscular dystrophy and 14 with facioscapulohumeral dystrophy through a battery of tests, all of which were negative. The authors conclude that there may be altered metabolism of myoglobin, for the normal value is not known.

Muscular dystrophy in later life and the condition described by Shy and McEachern[11] as menopausal dystrophy are forms of chronic polymyositis.[12]

Myasthenia gravis was described with progressive muscular dystrophy.[13] A sixty-two-year-old man had had progressive muscular dystrophy since childhood. He had wasting of muscles of the shoulder, arms and chest, as well as pseudohypertrophy of the legs. After an episode of influenza, ptosis, external ophthalmoplegia, bilateral facial weakness and difficulty in chewing and swallowing developed. He did well on neostigmine by mouth after a prompt response to parenteral administration. Four months later he had respiratory failure and died.

Muscular Dystrophy with Fat Vacuoles in Leukocytes

In a Dutch article,[14] 2 brothers, aged twenty-seven and twenty-four, were seen in 1951. Both had pseudohypertrophic muscular dystrophy of Erb and scapulohumeral dystrophy. The mother had gallstones, and the father was diabetic. There was no family history of dystrophy. A brother and sister were negative. In 1948 the older brother had complained of pains in the stomach. Fat vacuoles were found in the white cells of the blood at that time. Physical examination showed a heart murmur; reflexes were depressed, and strength poor. He had no muscle atrophy at that time. Thirty members of the family were examined, and 1 younger brother had the finding of fat vacuoles in the white cells. A glucose tolerance test was negative, as were tests for cholesterol, and the urine and feces were normal. Sternal-marrow puncture in 1951 showed fat vacuoles in cells of the myeloid series, with a normal differential count of myeloid cells. In 1951 muscle biopsy was typical of progressive muscular dystrophy. Vacuoles were seen in the leukocytes within the blood vessels. In a liver puncture there was no glycogen in the vacuoles. The authors believed that, normally, fat is not seen in the white corpuscles of circulating blood in muscular dystrophy. It is not seen in persons with good health but is seen with severe infections.

Muscular Dystrophy with Myoglobinuria Associated with Excessive Excretion of 17-Ketosteroids

A thirty-year-old man was studied who had muscular dystrophy and paroxysmal myoglobinuria after exercise.[15] He had large calves and bilateral pes cavus. There was a positive family history. The onset of dystrophy had been at eight years, and there was not enough wasting to account for his weakness. He was married and had a normal sex life. The potassium was 5.1 milliequiv. per liter at rest and 3 milliequiv. after exercise.

Case reports of 3 boys with similar symptoms were reported in the literature.

A defect in the enzyme system concerned with muscle metabolism may be a cause of muscular dystrophy. Disturbance of muscle-cell permeability causing loss of myoglobin and potassium that followed a game of squash indicated muscle breakdown in this period. Creatine was increased twenty-four hours after the game. An increase in ketosteroids was perhaps due to pituitary activity.

Wald and Lam[16] treated 15 patients with amino acid, folic acid and vitamin B_{12} and 15 with placebos, without improvement. The creatine and creatinine excretions of the former group were not altered.

Pregnancy and Muscular Dystrophy

According to Danish law, a woman is allowed to have her pregnancy terminated when there is a "pending danger that the child may, on account of hereditary deficiencies, be suffering from mental deficiency, epilepsy or a serious and incurable disease." Sterilization may be allowed when "a danger of affliction with hereditary taint is in favor of sterilization."

A study of 117 cases was regarded as indicating that both the dominantly inherited facioscapulohumeral type and the childhood lower-extremity type of muscular dystrophy warrant eugenic measures.[17]

It is well known in human genetics that a more benign type of disease is inherited dominantly, contrary to a more malignant type, which is inherited recessively. Various types may belong to the same nosologic unit. In childhood the lower-extremity type is more common than the facioscapulohumeral. Age of survival is 26.1 for the former, and 61.3 for the latter.

Creatine in Muscular Dystrophy

Benedict et al.,[18] using glycine N15, conclude that urinary creatine in progressive muscular dystrophy does not originate in muscle but represents freshly synthesized creatine that has been denied access to muscle.

Localized Muscular Atrophy in Diabetes

Hirson,[19] in the *Lancet,* describes 6 patients, all women beyond the menopause, with localized muscular atrophy. Although these patients had had diabetes, with injection of insulin, for some years the author considered the atrophy independent of insulin lipodystrophy. These areas of atrophy might be of the arms, legs or trunk and, though not symmetrical, were usually bilateral and did not follow any nerve distribution.

The striking loss of fat between the muscles of the upper arms is seen in one photograph. There were no fasciculations or nerve distribution to the areas of atrophy. The author cites 3 references in the French literature, before the days of insulin, to note that muscular atrophy had occurred in diabetes. The articles were published in 1883, 1890 and 1917. I found that these patients had muscle atrophy secondary to lesions of the nervous system.

When one is faced with one of these patients with so much asymmetrical but bilateral loss of subcutaneous tissue, it is natural that the first thought would be primary muscular atrophy. However, when one tests the strength of these muscles or looks at a microscopical section of muscle, it is normal.

Extensive insulin lipodystrophy is a rare disorder and only important from a cosmetic point of view, whereas the diagnosis of muscular atrophy carries a serious prognosis.

Myotonia Dystrophica

From the Tuscaloosa Veterans Administration Hospital comes a report of 3 brothers and a sister and a second cousin with myotonia dystrophica.[20] The patient in the Veterans Administration Hospital had been bed ridden before death. ACTH and cortisone had benefited the myotonia but not the weakness. The serum potassium was low after exercise. An interesting finding was that the father of the patient, according to the history, was thought to have had myotonia dystrophica, and the grandmother of all those mentioned had had an operation for cataract. All the others had the type of cataract seen in the disease. Three of the first 5 mentioned had abnormal electrocardiograms, and 2 had normal films of the skull.

Myotonia Dystrophica with Dyspnea, Cyanosis and Polycythemia

A fifty-seven-year-old man became aware of muscular weakness at the age of twenty-five. The weakness of the legs increased until he had been confined to bed for the last six years. His father and a brother and 2 sisters were affected by the same disorder. In addition to the muscular atrophy he had lenticular opacities, testicular atrophy and myotonia. He had cyanosis of the lips and nails, dyspnea and a red-cell count of 6,800,000, which are characteristic of the disease. By fluoroscopy the right leaf of the diaphragm was elevated, and movement of the entire diaphragm was limited. Cardiac-catheterization and pulmonary-function studies were done. It was thought that the weakness of the respiratory muscles had caused the impaired alveolar ventilation and incomplete oxygen saturation of blood in the pulmonary capillary. The polycythemia is a compensatory response to impaired oxygenation of blood within the lung.[21]

Caughey and Brown[22] reported 10 families in New Zealand consisting of 20 members, 15 with muscular atrophy and 5 with cataract alone. The endocrine functions were examined in 9 — 7 males and 2 females. There was gonadal atrophy in 5, with increased follicle-stimulating hormone. There was uniformly low 17-ketosteroid excretion. Two had myxedema. Parathyroid function was normal. There was normal electrolyte and carbohydrate function of the adrenal cortex. On occasion x-ray studies showed a small sella turcica, thickened calvarium and hyperostosis interna. There was a primary glandular defect consisting of atrophy of the androgen cells of the testis and of the adrenal cortex.

Radiologic changes in the skull in 13 cases of myotonia dystrophica were reported.[23] Most common were small sella turcica, thickening of the calvarium and hyperostosis interna. The sinuses were enlarged in some cases, and the mandible elongated in 2. These features should be accepted as some of the variable features of the disease.

Wohlfart[24] reported a series of muscle biopsies of which 5 showed myotonia congenita, and 18 myotonia dystrophica; 4 were normal, and 1 showed enlarged fibers in myotonia congenita. In myotonia dystrophica there were chains of nuclei in the center of the muscle cell, which showed different size of fibers. Wohlfart considers these two different diseases. One autopsy revealed myotonia dystrophica.

Disorders of Excitability and Contractility

Primary diseases of muscle are few in number, but both those mentioned below may indeed be due to disorders of the muscle cell itself. Myasthenia gravis, myotonia congenita, periodic paralysis and a disorder of glycogen breakdown described by McArdle are of this type. The literature of myasthenia gravis has been covered by Viets[25] in the *Journal.*

Myotonia Congenita

Zec et al.[26] made a study of the pathophysiology of myotonia congenita (Thomsen's). Seven patients

in one family were given curare. Intravenous injection of a third to a quarter of the dose given with anesthesia favorably affected the distal muscles for twelve days. The end plate is oversensitive to normal amounts of acetylcholine, and there is alteration of permeability of cell membrane.

Periodic Paralysis

Stevens[27] described familial periodic paralysis, myotonia, progressive amyotrophy and pes cavus in members of a single family. All 23 members of the family had familial periodic paralysis; 8 had atrophy of the skeletal musculature in early adulthood, 7 had enlarged calves in childhood, 4 had myotonia, 15 had pes cavus, 1 had myasthenia gravis, and 8 had areflexia. All had normal serum potassium values. Treatment with potassium was not helpful.

This paper contains a well chosen bibliography and excellent discussions of the relation of potassium to muscle disorders of many kinds, of the Friedreich syndrome to muscular dystrophy and of the endocrine glands to muscle disorders.

It is stated that familial periodic paralysis and myotonia have not been reported in the same patient. In these 4 patients the serum potassium was not reduced during an attack of periodic paralysis, and potassium therapy was not beneficial; in fact, it caused pain and stiffness of the lumbar and abdominal regions. This may have been true because of the presence of myotonia. Muscle biopsy of 1 patient was diagnosed as showing myotonia dystrophica.

Paralysis with Myotonia Dystrophica

The medical literature in Germany contains a description (1952) of an attack of paralysis in a twenty-six-year-old man with typical muscle and endocrine changes of myotonia dystrophica.[28] As far as I know this case is the first to be reported. (The 4 members of the large kindred described above did not have the clinical muscle atrophy or endocrine changes that are seen in myotonia dystrophica.) This case is abstracted, as follows:

The patient had tachypnea, tachycardia, tracheal rales and cyanosis of the lips. During the previous evening he had eaten eggs and sausage in a restaurant with companions. None had been sick. At 6 a.m. he tried to get out of bed and could not move his legs. Later, he could not move his arms. Micturition was not affected. He had had no previous attacks.

His mother and 2d brother had ptosis.

Physical examination showed a flaccid paralysis of the extremities, chest and back and the neck muscles. He had also lost reflexes, which returned the next day. The spinal fluid was normal. The blood sugar was 54 mg. per 100 ml. The white-cell count was 10,400, with 85 per cent neutrophils and 10 per cent stab forms.

The temperature, which was 98.2°F. on admission, went to 101.1°F. and then back to 97.5°F. on the 3d day. The nonprotein nitrogen was 31.1 mg., the albumin 3.45 gm., and the globulin 3.55 mg. per 100 ml. The potassium was 2.0 milliequiv. per liter, and the calcium 12.2 mg. per 100 ml. Hyperventilation, intramuscular injection of epinephrine and glucose by mouth did not cause an attack. The glucose tolerance curve was negative, and the urine was normal.

There was no kidney disease, hyperpotassemia, diabetes or hyperthyroidism. The only predisposing factors seemed to be a high-fat meal, sleep and the onset of an infection.

Progressive muscular dystrophy associated with periodic paralysis has also been reported in the Czech literature.[29] An abstract of this case is as follows*:

The patient's parents and 2 siblings were in good health.

At the age of 9 years, after an injection of diphtheria antitoxin, fever and paralysis of the legs for 4 days developed. Six months later the 1st episode of nocturnal paroxysmal paralysis occurred, consisting of his awaking at 3:00 a.m. with paralysis, associated with sweating lasting about 2 hours. Since then there had been repeated episodes, occurring irregularly at first, several months apart and at the time of admission 1 or 2 a month. These paroxysms appeared occasionally after excessive physical exertion and somewhat less frequently after a heavy meal, but for the most part were without apparent cause. In the afternoon or evening there were occasional feelings of heaviness in the extensor muscles of the legs, with some paresthesias and some general weakness. Occasionally, there was a feeling of weakness without paralysis. For the first few years the paralysis was more confined to the legs, but 1½ years after onset, the arms were also involved (but always to a lesser extent). There was some difficulty in turning the head during these attacks. There was never dysphagia or respiratory distress. Usually, the attacks lasted 2 hours, but the range was 1 to 9 hours.

From the age of 13 on he noted the onset of a "rocking gait" and found it more difficult to walk because of weakness of the legs and a typical "myopathic gait."

Physical examination showed a tall man with rather acromegalic features. Examination of the fundi was negative; there was diffuse muscle atrophy, not sparing the small muscles of the hands or those of the neck and throat. The muscles were both "hypotrophic and hypotonic." The scapulas were bilaterally winged. Deep tendon reflexes were diminished. Strength was generally decreased. There was atrophy of the back and abdominal muscles. The abdominal and cremasteric reflexes were present. The lower legs were severely affected, especially the quadriceps muscles. There was bilateral pes excavatum, with bilateral retraction of the toes. There was high curvature of the ribs, and curvature of the thoracic spine. He could stand only with aid, but once upright, he could stand without support. The genitalia showed normal development.

The blood pressure was 120/80, and the pulse 96. Spinal-fluid dynamics were normal. There was increased albumin and a positive globulin reaction. Blood counts were normal except for 3 or 4 per cent eosinophils, and electrolytes were normal, as was urinalysis. Normal vestibular function was observed. Skull films and an upper gastrointestinal series were normal. No persistent thymus could be discerned on chest films.

There was low electric reaction during an attack. It was stated that an attack was caused by the administration of 150 gm. of glucose. [The author then describes a typical attack.]

Treatment, consisting of potassium and vitamins, did not result in much change. The serum sodium was 177 milliequiv., the potassium 5.9 milliequiv., and the magnesium 1.1 milliequiv. per liter; the calcium was 10 mg. per 100 ml.

Bickerstaff,[30] who studied 2 patients in detail, stresses the permanent muscle and reflex changes in 1 case. The patient had atrophy of the thigh muscles, facial weakness and reflexes only on reinforcement. The author found many cases of muscle wasting in the literature; 2 of these authors reported pseudohypertrophy of the calves. Bickerstaff wondered if the

*Abstracted by Dr. Robert Petranic.

fundamental cause of the muscle weakness in familial periodic paralysis could be a structural abnormality in the elements responsible for contractility. If so, the variable biochemical findings and the permanent muscular atrophy would be more easily understood.

Hofman[31] and Painter[32] describe the appearance of periodic paralysis in 2 cases — after the onset of hyperthyroidism in 1 and after the development of diabetes in the other, which concerned a fifty-five-year-old man who had hypopotassemia, a sedimentation rate of 44 mm. per hour and an abnormal glucose tolerance curve; under treatment for diabetes these findings reverted to normal.

McArdle[33] reports for the first time a muscle disease due to a defect in glycogen breakdown. A thirty-year-old man had suffered from muscular pain, weakness and stiffness after exercise since childhood. Blood lactate levels fell during exercise, for the muscles were unable to break down glycogen. Ischemic exercises caused the same fall in blood lactate and an abnormal rise in serum potassium.

Discussion

Adams, Denny-Brown and Pearson,[1] in their pathological study of the diseases of muscle, analyze the nature and pathologic reactions of skeletal muscle and then present a detailed consideration of the pathology of the various diseases, including muscular dystrophies (generalized familial muscular dystrophy, dystrophia myotonica and ophthalmoplegia), toxic, metabolic and endocrine disorders (myohemoglobinuria and thyroid disease) and disorders of excitability and contractility such as myasthenia gravis, periodic paralysis, congenital myotonia, potassium paralysis, and myopathy due to a defect in muscle glycogen breakdown. They also consider differential diagnosis and methods of pathological study, including methods of obtaining and preparing muscle tissue for microscopical examination, biopsy and autopsy. Some of their discussion, which contains material of great significance, is quoted verbatim,* as follows:

[Muscular Dystrophy]

> . . . In those forms of dystrophy where heredity is strong, development early, and progression rapid, many of the muscle fibers remain small though otherwise well developed. Branching of apparently healthy fibers is common. In such forms infiltration of the endomysium by fat cells is far in advance of muscular atrophy. This appears to point to the existence of a defect in maturation of muscle fibers, and their supporting tissue, long antedating the onset of atrophy. . . .[1]

[Periodic Paralysis]

> . . . The primary disorder must be in the skeletal muscle fiber, to account for the complete inexcitability to either faradic or galvanic electrical stimulus, and for the occasional involvement of quite small and asymmetrical groups of muscles as in the case of Clark. The effect of glucose, muscular exertion, sleep, and similar procedures in precipitating attacks, and of potassium salts in relieving attacks, appear to be only through changes in the available reserves of potassium ions at times when the spontaneous liability to an attack is present. Jantz has claimed that striking changes occur in the ultrafiltrable fraction of potassium in periodic paralysis, not reflected in the total serum potassium. If this finding is confirmed it suggests that an abnormal degree of binding of potassium by large protein molecules occur in the paralytic attack.[25]

[Myotonia Congenita]

> . . . The cardinal feature of Thomsen's disease is the phenomenon of myotonia, in combination with a more or less pronounced muscular hypertrophy. . . . This isolation of the phenomenon of myotonia indicates that it is in the nature of an independent chemical contracture in a few of the fibers involved in the initiating excitation. It is not comparable to states of repetition of the initiating discharge following one excitation of the end-plate, as in veratrin contracture, but has the course and distribution of the cumulative effect of some by-product of the process of contraction (Denny-Brown and Foley). The value of percussion in eliciting localized myotonic discharge is related to the brief but relatively intense repetitive excitation which occurs when a muscle is percussed. It is comparable to a brief tetanization of faradic shocks at a rate of 300 per second. After an interval of 1/10 second a number of the muscle fibers in the excited fasculus then exhibit a prolonged burst of myotonia . . . The immediate contraction elicited by percussion differs in no way from that in normal muscle.
>
> The phenomenon of myotonia, thus defined, is an independent by-product of the preceding contraction, affects only a small number of the muscle fibers initially excited, and is itself relatively weak in contractile force. Yet in Thomsen's disease, but also to a lesser and more localized extent in some cases of dystrophia myotonica, the observer is impressed by the active spasm which impedes the initiation of movement in the prime mover, and at the cessation of effort involves whole groups of muscles not active in the initial effort. It may at first appear that the widespread after-spasm is an aspect of the effort to relax. With a cooperative patient, however, it is clear that simple relaxation of the grasp of the hand can alone set up an involuntary spasm in the forearm or whole limb, in flexors and extensors alike, more powerful than the original movement, and incapable of modification by the patient. Such spasms are, in fact, the chief disability, for they are responsible for the sudden immobilization of part or whole of the musculature which temporarily disables the patient. Denny-Brown and Nevin showed that this after-spasm, in muscles remote from the prime mover, was associated with an intense discharge of the large rhythmical action potentials of motor unit activity, and was not necessarily preceded by motor innervation. . . . It is determined by activity of certain specific muscles, in which muscular myotonia was well developed and can therefore be demonstrated most clearly in dystrophia myotonica. For example, when myotonia could be demonstrated only in the intrinsic muscles of the hand, such an after-spasm appeared in flexor carpi ulnaris only following a grasp of the hand, but failed to appear after ulnar deviation. It did not appear at all in this muscle after a grasp of the fingers following novocain block of the median and ulnar nerves at the wrist. Reflex after-spasm is easily fatigued by repetition yet the peripheral myotonia still remains and can be elicited by percussion. Such muscular myotonia can then be seen to offer only feeble resistance to antagonistic muscle. In congenital myotonia the response to percussion is more powerful, but electromyographically combinations of peripheral and central action potentials are also found to impede movement. From such observations Denny-Brown and Nevin concluded that the generalized after-spasms of Thomsen's disease (as distinct from the delay in relaxation of prime movers) are a reflex effect produced by an abnormal afferent proprioceptive discharge determined by myotonia in the prime movers. Though the disorder is primarily muscular, its reflex effects are therefore of

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considerable importance in symptomatology. Such effects also afford the only evidence at present available that the proprioceptive end-organs are affected by the disease.

The high intensity of neuronal discharge thus caused in patients suffering from myotonia provides adequate physiologic explanation for hypertrophy of the muscle fibers concerned.[36]

Histology

In myotonia congenita (Thomsen's disease) biopsy does not reveal any abnormality other than hypertrophy of all fibers. . . .[37]

Conclusion [of Chapter on Miscellaneous Diseases]

. . . The remaining miscellaneous diseases comprise disorders of neuromuscular transmission, both at the motor end-plate (myasthenia gravis, botulism) and in excitable membrane of the muscle cell (periodic paralysis, hyper-potassemia). There appears to be a disorder of the contractile mechanism in adrenal insufficiency, and possibly in some hyperthyroid syndromes, myotonia, hypertrophia musculorum vera; a disorder of glycogen storage in von Gierke's disease, of fat storage in hyperthyroidism, of pigmentary metabolism in myohemoglobinuria, and of the constituents of the connective and aponeurotic tissues with contractures in Addison's disease and myositis ossificans. Such a list not only illustrates the many different metabolic processes in which muscular tissue is engaged, but also stresses that contraction is only one of the many functions of muscle.

We have indeed considered the feasibility of describing these diseases in such physiologic groups. Further consideration, however, makes it clear that such a plan, though attractive, is premature, and gives a misleading impression of finality. Close inspection of the relevant data concerning each of these diseases discloses the extremely hypothetical nature of such grouping, and of its basis in current schemes of fundamental physiology. The chief purpose of this review will have been well served if it stimulates and leads to a further investigation toward a more complete definition of muscular activity and its disorders.[38]

Summary

Since the last Medical Progress report on diseases of muscle in 1951 there have been 1 book, 3 conferences sponsored by national societies for research in muscular dystrophy and a number of other contributions. Among these are the reports of muscular dystrophy combined with many varieties of muscle disease, Gerard's work with tissue cultures and the opinion voiced by several authors that in myasthenia gravis, periodic paralysis and myotonia congenita the disorder lies not in the transmission of the nerve impulse but in the excitability or contractility of the muscle cell itself.

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MEDICAL INTELLIGENCE

PRIMIDONE (MYSOLINE) IN THE TREATMENT OF EPILEPSY*

Results of Treatment of 486 Patients and Review of the Literature

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THE first report dealing with the use of primidone (Mysoline) in the treatment of epilepsy was presented in 1952 by Handley and Stewart.[1] Many other investigators[2-27] subsequently used this drug for the control of epileptic seizures. In 1953 Doyle and Livingston[8] analyzed the results obtained in 100 patients with epilepsy who had been given primidone for periods of three months to one year. The purpose of the present paper is to report our findings in a larger group of patients who received this drug for a much longer period.

MATERIAL FOR STUDY

The drug was administered to 486 patients who suffered from epileptic seizures of various types.

Two hundred and ninety-four of these patients had been receiving maximum dosages of one or more anticonvulsants (phenobarbital, Mebaral, Dilantin, Mesantoin, Paradione or Tridione) for at least six months before the primidone was prescribed. In 212 of these 294 patients the previous medication failed to control completely but did reduce the frequency of the seizures to some extent. These 212 patients were given primidone in addition to the same dosage of the previous medication throughout the entire observation period. In the other 82 cases the previous medication was completely ineffectual. During the first month these 82 patients received primidone in addition to the same dosage of the previous medication. During the subsequent two months the previous medication was gradually withdrawn. Thereafter, these 82 patients received primidone only.

One hundred and ninety-two of the 486 patients included in this study had never been treated previously with any form of anticonvulsant therapy. These patients received only primidone during the entire observation period.

Three hundred and eleven of the 486 patients had pure major motor (grand-mal) seizures, 53 had minor motor spells, 42 had petit-mal spells, 41 had psychomotor seizures, and 39 had 2 or more of the various types of seizures (mixed epilepsy).

Two hundred and fifty-two of these patients ranged in age from one to fourteen years, and 234 were over fifteen years of age.

TABLE 1. *Dosage.**

AGE	INITIAL DOSAGE	MAXIMUM DOSAGE
yr.		
<3	62.5 mg. twice daily	125 mg. 4 times daily
3-6	125 mg. twice daily	250 mg. 4 times daily
6-14	250 mg. twice daily	500 mg. 3 times daily
>14	250 mg. 3 times daily	500 mg. 4 times daily

*Drug dispensed in 250-mg. tablets.

DURATION OF TREATMENT AND DOSAGE

The duration of therapy ranged from six months to three years. Two hundred and fifty-six patients have been receiving the drug continuously for two or three years.

The dosage administered varied from 375 mg. (1½ tablets) daily to 2000 mg. (8 tablets) daily (Table 1). The drug was given in 2 to 4 doses over the course of the day.

TABLE 2. *Results in 192 Patients Who Had Not Been Treated Previously with Any Form of Anticonvulsant Therapy.**

TYPE OF SEIZURE	NO. OF PATIENTS	ATTACKS CONTROLLED	ATTACKS MARKEDLY IMPROVED	ATTACKS IMPROVED	FAILURE OF THERAPY
		NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS
Major motor (grand mal)	97	55	11	10	21
Petit mal	26	0	0	0	26
Psychomotor	20	0	0	0	20
Minor motor	32	0	0	0	32
Mixed†	17	0	5	3	9
Totals	192	55	16	13	108

*Patients receiving only primidone throughout observation period.
†Only major motor seizures affected favorably.

RESULTS

Primidone was effective only in the treatment of major motor (grand-mal) epilepsy (Tables 2-4). The major attacks were controlled completely in 55 (57 per cent) of the 97 patients who had not been treated previously with any type of anticonvulsant therapy (Table 2). These patients received only primidone

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throughout the entire observation period. The major seizures were controlled completely in 53 (28 per cent) of the 191 patients in whom the frequency of seizures had been partially reduced with maximum dosages of other anticonvulsant drugs (Table 3). These patients received primidone in addition to the

TABLE 3. *Results in 212 Patients Whose Seizures Were Controlled Partially with Maximum Dosages of Other Anticonvulsant Drugs.**

TYPE OF SEIZURE	NO. OF PATIENTS	ATTACKS CONTROLLED	ATTACKS MARKEDLY IMPROVED	ATTACKS IMPROVED	FAILURE OF THERAPY
		NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS
Major motor (grand mal)	191	53	22	18	98
Petit mal	3	0	0	0	3
Psychomotor	6	0	0	0	6
Minor motor	4	0	0	0	4
Mixed†	8	0	3	2	3
Totals	212	53	25	20	114

*Patients receiving primidone in addition to same dosage of previous medication throughout observation period.
†Only major motor seizures affected favorably.

same dosage of the previous medication throughout the entire period of treatment. The seizures were controlled completely in 4 (17 per cent) of the 23 patients who were entirely refractory to maximum dosages of other anticonvulsant drugs, including phenobarbital and Dilantin (Table 4). For the first

TABLE 4. *Results in 82 Patients Whose Seizures Were Completely Refractory to Maximum Dosages of Other Anticonvulsant Drugs.**

TYPE OF SEIZURE	NO. OF PATIENTS	ATTACKS CONTROLLED	ATTACKS MARKEDLY IMPROVED	ATTACKS IMPROVED	FAILURE OF THERAPY
		NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS
Major motor (grand mal)	23	4	3	3	13
Petit mal	13	0	0	0	13
Psychomotor	15	0	0	0	15
Minor motor	17	0	0	0	17
Mixed†	14	0	4	2	8
Totals	82	4	7	5	66

*During 1st mo. patients given primidone in addition to same dosage of previous medication; during subsequent 2 mo. previous medication gradually withdrawn; thereafter, only primidone given.
†Only major motor seizures affected favorably.

several months these patients received both the previously ineffective medication and primidone. Thereafter, they were given the new agent only.

None of the patients who had other types of seizures (petit mal, minor motor or psychomotor) were benefited significantly by the drug.

UNTOWARD REACTIONS

The most common side reaction encountered was drowsiness, which occurred in 160 patients (Table 5). It varied in degree from a mild, transient sleepiness to a severe lethargy. In the majority of cases the drowsiness appeared within the first days of the beginning of primidone therapy. In many cases it came on after the first few doses were taken. Several patients stated that they slept for approximately twenty-four hours after taking single tablets. In 127 patients the drowsiness disappeared spontaneously within several weeks of its onset, and treatment with the same dosage of the drug was not interrupted. In 33 patients the dosage necessary to control the convulsions produced such a severe lethargy that the drug had to be discontinued.

Dizziness was reported in 22 patients, and ataxia was noted in 19. It was necessary to discontinue the

TABLE 5. *Untoward Reactions Manifested by 211 of 486 Patients Treated.*

REACTION	NO. OF PATIENTS	DRUG DISCONTINUED BECAUSE OF REACTION
		NO. OF PATIENTS
Drowsiness	160	33
Dizziness	22	9
Ataxia	19	4
Nausea and vomiting	4	0
Skin rash*	2	0
Personality change	2	0
Diplopia	2	0
Totals	211	46

*Primidone discontinued when rash appeared; same dosage given again after rash had completely cleared up; rash did not reappear in association with 2d administration of drug.

therapy in 9 of the patients who complained of dizziness and in 4 who presented ataxia. In the remainder of the patients, the dizziness and ataxia cleared up spontaneously within one or two weeks, and treatment with the same dosage was not interrupted.

Generalized morbilliform skin rashes occurred in 2 patients six and ten days respectively after the first dose. In both, the rash disappeared within ten days of withdrawal of the drug. The same dosage was given again to both patients, and the rash did not reappear.

Diplopia occurred in 2 patients, personality changes in 2, and nausea and vomiting in 4. These disturbances were transient and of little consequence.

Routine blood counts and urinalyses were made monthly on the first 200 patients included in this report for an interval of a year and a half. No abnormalities were encountered in any case.

DISCUSSION

The results of this study, and also of the previous one,[8] indicate that primidone is primarily of value in the treatment of major motor (grand-mal) epilepsy.

Many other investigators[1-3,5,7,9,10,13,18,19,22-27] have had similar experiences. None of our patients with petit-mal, minor motor or psychomotor seizures were helped significantly by this drug. However, other workers[2,5,7,15,27] have reported good results in petit-mal and psychomotor epilepsy.

Most investigators agree that untoward reactions occur in a high percentage of patients receiving the drug. They were encountered in 211 (43 per cent) of our 486 patients. Sciarra et al.[19] reported that 1 or more side effects appeared in 65 (82 per cent) of their 79 patients. In addition to the untoward reactions observed by us (Table 5) a wide variety of disturbances have been reported: edema of the eyelids,[19] painful gums,[19] sexual impotence,[19] slurred speech,[13,19,21] nystagmus,[11,19] paranoid psychosis,[2,7,18] headaches,[21] polyuria[2] and abdominal pain.[15]

Drowsiness occurred in 160 (33 per cent) of our patients and was by far the most frequent disturbance encountered both in our series and in those reported by others.[2,5,7,9,11-13,21,22] This disturbance cleared up spontaneously without reduction in dosage in the majority of our cases (Table 5). Timberlake and his co-workers[25] suggested that the drowsiness might be minimized if treatment was started with half a tablet (125 mg.) at bedtime and the dose very gradually increased thereafter as indicated.

No hematologic disturbances were encountered in any of our patients. However, 2 cases of leukopenia have been reported.[15,25] To our knowledge no irreversible toxic disturbances have been observed.

In conclusion, it is our belief that primidone has received sufficient clinical trial to be considered a safe and effective drug for the treatment of major motor (grand-mal) epilepsy. Although side reactions occur in a large percentage of patients, these are for the most part mild and transient and do not commonly necessitate withdrawal of the drug.

Summary

Four hundred and eighty-six patients with epilepsy were treated with primidone (Mysoline) for periods ranging from six months to three years.

The literature is reviewed.

Mysoline was effective only in controlling major motor (grand-mal) seizures in our group of patients. Other investigators have reported good results in petit-mal and psychomotor spells.

Drowsiness was the most frequent side reaction observed.

No irreversible toxic disturbances were encountered.

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QUADRIPLEGIA, HYPOPOTASSEMIA, AND HYPERCHLOREMIC ACIDOSIS AFTER BILATERAL URETEROSIGMOIDOSTOMY*

John F. Loughlin, M.D.†

TOGUS, MAINE

THE occurrence of hyperchloremic acidosis after bilateral ureterosigmoidostomy has been reported frequently and has caused much medical interest and many changes in surgical technics.[1-3] The underlying physiologic features that account for this picture center around two general concepts. The first concerns intestinal absorption of urinary constituents and selective absorption of chloride, sodium and chloride as sodium chloride and ammonium and chloride, and the second abnormalities in function of the renal tubules. According to Lapides[2] such abnormalities do not occur if renal function is good. In some cases with presumably normal preoperative renal function hyperchloremic acidosis has developed postoperatively, and a rapid reversal of the abnormality has followed prompt and proper treatment. In such cases the condition appears to have developed mostly on the basis of intestinal absorption of urinary constitu-

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ents. In others, such as the one presented below, impairment of the renal tubules appears to be a prominent cause. Hypopotassemia, in association with this syndrome, has been described by several authors. Matern[4] reported a case of hypokalemia and hyperchloremic acidosis after bilateral ureterosigmoidostomy with the typical electrocardiographic signs of hypopotassemia. Clinically, there was lethargy, weakness and drowsiness before successful treatment. Foster, Drew and Wiss[5] presented a case of hyperchloremic acidosis and potassium deficiency that followed bilateral ureterosigmoidostomy. The patient, who was in a stuporous state and acidotic, was clinically well within forty-eight hours of the start of treatment. Electrocardiograms revealed a pattern consistent with hypokalemia, and the serum potassium was depressed. The occurrence of muscle paralysis in such cases has not been commonly reported. Brown, Currens and Marchand[6] presented 2 cases of muscular paralysis and electrocardiographic abnormalities associated with potassium loss. These patients gave evidence of chronic renal disease but had no surgical diversion of the urinary stream to the intestinal tract. Diefenbach, Fisk and Gilson[7] presented a case of hyperchloremic acidosis with hypopotassemia and muscle paralysis sixteen months after bilateral ureterosigmoidostomy. Their case was quite similar to the one encountered at this hospital although recovery from paralysis, electrocardiographic abnormalities and hypopotassemia was much more rapid. Skanse and Widén[8] report a similar case, in which potassium deficiency and quadriplegia followed an intravenous pyelogram taken fourteen months after ureterosigmoidostomy. Hyperchloremia was not noted in this case, and the paralysis responded to therapy.

Hypopotassemia in these cases appears to be due

TABLE 1. *Effect of Treatment.*

DATE	SYMPTOMS & SIGNS	BLOOD UREA NITROGEN	CARBON DIOXIDE	POTASSIUM	SODIUM	CHLORIDE	ELECTROCARDIOGRAM	TREATMENT
		mg./100/ml.	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*		
9/29*	Generalized weakness, patient barely able to move extremities; finger motion almost gone; definite impairment of intercostal muscles.	57.0	13.0	3.5	142.0	140	Abnormal record; varying atrioventricular block; broad, flat T waves; prolonged QT interval; delayed interventricular conduction consistent with low potassium.	2000 ml. of 1/6 molar lactate; 140 milliequiv. of potassium chloride intravenously; 100 ml. of bouillon every hr.
9/30†	Patient able to move fingers, toes, ankles & wrists; minimal motion of forearms, shoulders & legs; impairment of chest movement not improved.	57.0	22.0	3.3	142.0	120	Unchanged	10 ml. of calcium gluconate; 1000 ml. of Darrow's solution; 0.5 gm. of sodium bicarbonate 4 times daily; 1000 ml. of 5% dextrose in water, with 40 milliequiv. of potassium chloride; 100 ml. of bouillon every hr.
10/1	Further improvement in movement of extremities; patient able to move shoulders & legs well; intercostal motion good; fairly strong hand grasp; patient still unable to walk or stand.	—	23.0	—	—	118	Borderline (minimal changes suggestive of potassium deficiency)	1000 ml. of 5% dextrose; 400 ml. of bouillon; low-salt diet; forced fluids.
10/2	Patient out of bed & walking about ward without any noticeable weakness.	27.0	—	—	—	—	Borderline (minimal changes suggestive of potassium deficiency)	Low-salt diet
10/3	—	27.0	23.0	3.5	139.4	118	Borderline	—
10/9	—	—	—	—	—	—	Within normal limits	—
10/14	—	37	—	3.1	142.3	—	—	—
11/16	(Follow-up examination after discharge)	62.8	16.6	3.16	135.0	139	—	—
12/29‡	—	60.9	22.0	3.6	136.0	125	—	—
2/19	—	19.0	25.0	4.7	141.0	112	—	—
3/8	—	31.0	22.0	4.7	137.0	100	—	—
3/10	(Follow-up examination after discharge)	37.0	25.0	4.8	140.0	122	—	—

*Day of admission.
†Calcium 9.6 mg. per 100 ml. on this day.
‡Readmission for transplant of rt. ureter to skin (performed in January, 1954).

to a combination of deficient potassium intake and potassium loss by vomiting, forcing of fluids and urinary excretion in association with chronic renal disease and acidosis. Hypopotassemia and an inability of the kidneys to conserve potassium have been noted in cases of chronic renal disease.[9-12] In addition, Albright and Reifenstein[13] have described renal acidosis with "tubular insufficiency without glomerular insufficiency" in which potassium as a base was excreted in excess in the urine because of inability of the kidneys to make ammonia and excrete an acid urine, and with sufficient potassium loss, weakness and muscle paralysis.

Case Report

R.P., a 43-year-old veteran, was admitted at 2:15 p.m., on September 29, 1953, to the General Medical and Surgical Hospital, United States Veterans Administration Center, Togus, Maine, complaining of vomiting, weakness and lassitude that had begun 3 days previously and had developed into complete paralysis of the extremities. On September 28, he "vomited all day." Whenever he attempted to ingest food he vomited. It was difficult to ascertain exactly how many times this took place, but vomiting episodes happened at least 7 or 8 times. On the day of admission vomiting continued, and the extremities became so weak that he could not get up and walk, being hardly able to move either arms or legs. Cystectomy and right-sided ureterosigmoidostomy had been performed on April 30, and a left-sided ureterosigmoidostomy on July 2, for papillary carcinoma of the bladder. At that time it was noted that there was slight decrease in function of the right kidney and moderate decrease of function of the left. Laboratory studies at the time of discharge revealed a blood urea nitrogen of 14 mg. per 100 ml. and a carbon dioxide of 27 milliequiv. and a chloride of 112 milliequiv. per liter. He was advised to remain on a low-salt intake and to empty the rectosigmoid frequently to prevent stasis of urine and accumulation of chloride. He had felt quite well subsequently until 3 days before the onset of the symptoms mentioned above. It was probably significant that for a while before the recent symptoms began he did not get up nightly to void as he had done previously in accordance with instructions.

Physical examination showed a well developed and well nourished man with signs of general weakness. Voluntary motor power was almost completely absent. There was essentially no finger or toe motion remaining. Tendon reflexes were markedly diminished but were present. Sensory examination revealed no abnormalities. The heart and lungs were normal, and the blood pressure was 140/60. He was conscious and mentally alert. Breathing was mostly diaphragmatic, with weak intercostal motion. There was no cranial-nerve involvement or spinal-fluid abnormality.

The patient had hyperchloremic acidosis on entry, and it was believed that the muscle paralysis was due to hypopotassemia. An electrocardiogram was consistent with this impression, revealing varying atrioventricular block, and broad and flattened T waves, with a prolonged QT interval and delayed interventricular conduction. Examination of the blood showed a white-cell count of 10,450 and a hemoglobin of 12.5 gm. per 100 ml. The blood urea nitrogen was 57 mg. per 100 ml., and the potassium 3.5 milliequiv., the sodium 142.3 milliequiv., the carbon dioxide 13 milliequiv., and the chloride 140 milliequiv. per liter.

Treatment consisted of 1/6 molar lactate solution intravenously, with added potassium chloride, Darrow's solution intravenously, hourly feedings with bouillon for its potassium content, oral administration of sodium bicarbonate and immediate insertion of a rectal tube. Prophylactic penicillin and urinary antiseptics were given in addition. On this regimen improvement very slowly occurred, and by 8:30 a.m. the next day the patient could move fingers and toes, ankles and wrists, but he still had only minimal movement of the forearms, shoulders, legs and trunk. Chest motions did not seem to have significantly improved. By the following day he had a fairly strong hand grasp and could move the head and extremities without significant impairment. He was unable to walk, however. On the next day he could walk about the ward without any weakness, and no muscle paralysis was noted. The relation of symptoms, electrolyte findings and electrocardiograms to treatment is presented in Table 1.

Discussion

The recovery periods for clinical symptoms, electrocardiographic abnormalities and serum potassium determinations are compared in Table 2. A great difference in the time required for clinical, electrocardiographic and serum potassium abnormalities to recover is evident. In the case reported above the serum potassium was never very low and, even after electrocardiographic and clinical improvement, showed one determination lower than that noted on admission. By contrast the case reported by Diefenbach et al.[7] demonstrated clinical and electrocardiographic recovery at the end of an hour after 1500 ml. of Darrow's solution intravenously, and yet the serum potassium at the end of that time was at the low level of 2.46 milliequiv. per liter.

Table 2. *Comparative Periods Required for Symptoms, Electrocardiograms and Potassium to Return to Normal.*

Source of Data	Interval before Clinical Symptoms Returned to Normal	Interval before Correction of Electrocardiographic Abnormalities	Serum Potassium	
			value	interval since treatment
			milliequiv./liter	
Present case	3 days	6 days	3.5 to normal	4 mo.
Diefenbach et al.[7]	1 hr.	1 hr.	2.46	1 hr.
Skanse & Widén[8]	12 hr.	"Few days"	2.3 to normal	"Few days"
Matern[4]	12 hr. (weakness)	48 hr.	2.5 to normal	5 days

Summary

A case of quadriplegia in a patient with renal disease after bilateral ureterosigmoidostomy is presented. It is of interest that serum potassium determinations were moderately low for four months after clinical recovery until one ureter was brought out to the skin.

In a review of this case and similar cases reported in the literature a definite trend in treatment response was noted. Clinical improvement occurred first, and was followed by improvement in the electrocardiographic picture and lastly by a rise of the serum potassium to normal levels. No quantitative relation between the degree of muscle paralysis because of hypopotassemia and the electrocardiographic findings was demonstrated.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42071

PRESENTATION OF CASE*

A seventy-three-year-old man entered the Emergency Ward complaining of epigastric pain.

Three days previously while digging in his garden, he was seized with severe pain in the upper abdomen that radiated to the interscapular region and extended along both costal margins. According to his physician the pain was substernal although the patient denied it. At that time physical examination was negative, and two electrocardiograms were reported as normal. He had two or three episodes of vomiting, with some nausea. He was given an enema, which returned blood at the end. No stools but gas and small amounts of blood were passed thereafter. He continued to have mild abdominal pain, felt tired and was anorectic. He had no fever until the evening before admission, when his temperature gradually rose to 102°F. He pointed to the right upper quadrant as the site of the most severe pain during the twenty-four hours before admission. On the day of admission, he had epigastric pain, belching and bloating. He was admitted for study.

On physical examination, he was well developed and well nourished and looked much younger than his stated age. The skin was warm, sweaty and not icteric. The lungs were clear. The heart was slightly enlarged to the left, and there was a Grade 1 apical systolic murmur. The abdomen was thought to be slightly tender in the right upper quadrant, but there was no spasm or guarding. The remainder of the abdomen was normal, with no palpable masses or organs. Peristalsis was normal. Rectal examination revealed a hard, polypoid mass on the left anterior wall of the rectum, just inside the anal canal, that bled easily. The prostate was enlarged, without nodularity. Neurologic examination was negative.

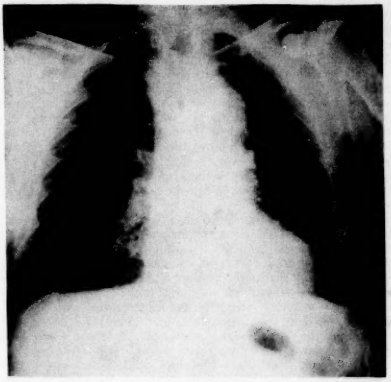

FIGURE 1. *Anteroposterior View of the Chest. The lungs are emphysematous. The left ventricle is prominent, and there is widening of the thoracic aorta, with some shagginess of the region of the proximal descending portion.*

The temperature was 102°F., the pulse 100, and the respirations 24. The blood pressure was 180 systolic, 130 diastolic.

The urine was amber and alkaline, had a specific gravity of 1.010 and gave a ++ test for albumin and negative tests for sugar, bile and acetone; the sediment contained 50 red cells, no white cells and rare hyaline and granular casts per high-power field. Examination of the blood revealed a white-cell count of 17,500

*Televised from the Ether Dome of the Massachusetts General Hospital to the Hotel Statler, Boston, for the annual meeting of the Massachusetts Medical Society, May 20, 1954. (Televised by Radio Corporation of America through the courtesy of the Wyeth Laboratories.)

and a hemoglobin of 12.5 gm. per 100 ml. The nonprotein nitrogen was 25 mg., and the bilirubin 1.1 mg. per 100 ml., and the serum amylase 21 units. The prothrombin time was 15 seconds (normal, 12 seconds). An electrocardiogram showed a normal rhythm, axis and PR interval. The T waves were upright and the QRS waves somewhat slurred in Leads 1, 2, 3, aVL and aVF; the T waves were low upright in Lead V_1 and upright in Leads V_2 through V_6; the S waves were somewhat high in Leads V_2, V_3, and V_4. A roentgenogram of the chest disclosed

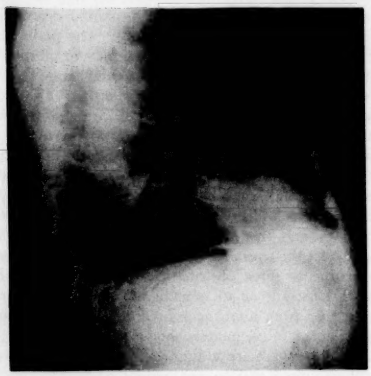

FIGURE 2. *Lateral View of the Chest.*

emphysematous lungs with accentuated lung markings, some enlargement of the heart in the region of the left ventricle and an elongated aorta, with widening and tortuosity of the transverse portion (Fig. 1 and 2). Films of the abdomen showed gas in the large and small bowel without abnormal distention. No abnormal masses were seen, and no stones were present in the right upper quadrant or along the course of the ureters. A Graham test revealed no contrast medium within the gall bladder; no opaque stones were seen, though the region was partially obscured by the contrast medium in the colon. On barium-enema examination the rectum ballooned out well, but the barium was held up at the distal sigmoid. On a second attempt, barium entered the distal descending colon before it was again expelled. Diverticula with no evidence of diverticulitis were seen.

The patient was given penicillin and streptomycin on the second hospital day and the temperature fell to normal although the white-cell count rose to 25,200, with 85 per cent neutrophils. The hemoglobin was 15.5 gm. per 100 ml. He had several attacks of abdominal pain, which he had difficulty in locating but which seemed to be most severe in the right upper quadrant. There was slight but definite tenderness in the right upper quadrant. By the third hospital day the abdominal pain was less, and the temperature continued normal. The white-cell count fell to 15,800. Sigmoidoscopy showed a small, red-purple, smooth-surfaced lesion, with a blood clot at the tip, that measured 1.5 by 1.0 cm. and was biopsied. The pathological report was: acute and chronic inflammation, with granulation tissue. During the ensuing days the patient was disoriented at night, and complained of recurrent attacks of abdominal pain that he said was localized in the right upper quadrant. On the seventh day an operation was performed. The surgeon's description of the operation was as follows:

> The patient was first placed in lithotomy position. The anal canal was dilated, and it was found that there had been an abscess in the anterior wall of the rectum that had drained spontaneously. This appeared inflammatory, without any evidence of neoplasm.
>
> Thereafter, a right upper paramedian incision was made. The gall bladder contained a number of palpable stones, but there was no evidence of acute inflammation, and a very careful examination of the entire peritoneal cavity was entirely negative. Inspection and palpation of the stomach, small and large bowel, liver, spleen and aorta were within normal limits. It seemed questionable that there was enough disease to account for the symptoms, but it was considered wise to proceed with an exploration of the biliary tree. Accordingly, the gall bladder was mobilized and, after individual clamping of the cystic duct and artery, removed from below upward. Because of the finding of stones, the common duct was opened, and numerous bits of gravel and clear bile were aspirated. The common duct was closed about a No. 12 T tube. A cigarette wick was placed in Morrison's pouch and, with the T tube, was brought out through a stab wound below the costal margin.

The pathological report was chronic cholecystitis, cholelithiasis and adenomatous polyp of the rectum. The patient withstood the operations well, and on the second postoperative day, he was allowed to walk with help. About thirty minutes later, he rolled to the side of the bed and cried out that he had "horrible" pain in the left side of the chest. In the next few minutes he became comatose. On examination, he was cyanotic, sweaty and pulseless. The neck veins were flat. Breath sounds were absent in the left side of the chest from the seventh thoracic vertebra to the base; there was good aeration on the right. The trachea was shifted to the left. Bronchoscopy was carried out, with removal of a moderate quantity of liquid secretions from the left bronchus. The left lung seemed slightly better aerated after this, but no breath sounds were heard at the left base. Despite supportive measures he died two hours later.

DIFFERENTIAL DIAGNOSIS

DR. OLIVER COPE*: Sometimes the written record does not contain every detail.

DR. BENJAMIN CASTLEMAN: Perhaps Dr. Kranes can answer your questions.

DR. COPE: Dr. Kranes, did the attack of pain in

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the upper abdomen come on while the patient was actively digging?

DR. ALFRED KRANES: I cannot recall whether he was actively digging, but he had been working in the garden when the pain occurred.

I think it is fair to amplify the history: the first episode of pain was in the back rather than in the abdomen; after pain had been present in the back for an hour or so it began in the abdomen.

DR. COPE: Had he had any previous rectal symptoms?

DR. KRANES: His family told me that during the week before the attack he had been having some "trouble with his bowels." The exact nature of the trouble was never quite clear, but I think it was constipation. They also reported that he had a little rectal bleeding on several occasions during that week.

DR. COPE: The rectal symptoms, then, started before the admission.

DR. KRANES: There are additional modifications of the record that I think should be made. Apparently I did not enter all the details in the patient's record. Dr. Castleman is often accused of withholding information. That is not true in this case. There was a shift of the pain from the right upper quadrant, which was its main site during the first forty-eight hours, to the left side of the abdomen thereafter. This pain was paroxysmal. It was sometimes in the left upper quadrant and at other times in the left lower quadrant. Unfortunately, I cannot give details about the nature of that pain because I was not able to speak Portuguese, and he spoke very little English.

DR. COPE: We have, then, two helpful leads amplified by Dr. Kranes.

May I ask for an impartial cardiologist to read the electrocardiographic tracing and give his opinion?

DR. EDWIN O. WHEELER: The electrocardiograms are within normal limits. Should you like that in more detail?

DR. COPE: Obviously, the electrocardiogram is very important evidence. The two electrocardiograms that were taken before the patient entered the hospital were interpreted as normal, and I expect that they were taken to determine whether he had had a coronary accident. On the other hand, as I understand it, Dr. Wheeler, there may be even later changes; therefore, the electrocardiograms taken soon after admission would be important evidence. Do these small changes in details that you see raise your suspicion of any abnormality in a patient seventy-three-years of age?

DR. WHEELER: These small questionable abnormalities indicate possible or questionable left ventricular hypertrophy.

DR. CASTLEMAN: I was about to say the official interpretation was left ventricular hypertrophy, which could be due to hypertensive heart disease.

DR. COPE: The patient had hypertension so that the findings were consistent with that.

It would be helpful if the radiologist would show the films.

DR. JOSEPH HANELIN: The posteroanterior and lateral projections of the chest, taken on the day of admission, show a mild degree of pulmonary emphysema. Otherwise, the lungs are clear. The heart appears to be slightly enlarged in the region of the left ventricle. The aorta is definitely widened and tortuous. The transverse portion appears to be somewhat more greatly dilated than the remainder of the thoracic aorta. There is also some question of a mild degree of shagginess along the proximal descending portion in this area (Fig. 1 and 2). The plain films of the abdomen, also taken on the day of admission, show gas scattered in the small and large bowel, without any unusual degree of distention. There are no visible stones. The next day a Graham test was attempted; as the protocol indicated, there was no contrast medium within the gall bladder. Three days after admission two attempts were made to do a barium-enema examination; even though a balloon catheter was utilized, it was not possible to fill the colon beyond the distal descending portion. I cannot detect the cause for failure of filling. It may have been due to some obstruction that we are not able to demonstrate or to some irritative process in the rectum or from anal incontinence. In the spot films diverticula are adequately shown. In addition to the diverticula, there are a number of filling defects within the sigmoid that suggest polyps.

DR. COPE: Is the spasm that was encountered the kind of spasm one would expect to find with diverticulitis?

DR. HANELIN: Yes; although there are diverticula, some of the other cardinal signs of diverticulitis are absent. This does not rule out diverticulitis.

DR. COPE: Your amplification of the findings in the chest is very helpful. Can you exclude a shadow behind the heart consistent with either a small abcess or infarction? I see none.

DR. HANELIN: I do not see anything that I should consider to be either infarction or an abscess. There is some blunting of the left costophrenic sulcus posteriorly, which may be the result of old pleural thickening. Without previous films it is impossible to evaluate this as an isolated finding.

DR. COPE: The rise in the hemoglobin from 12.5 to 15.5 gm. per 100 ml. is quite extraordinary unless the patient had received a transfusion. Did he receive a transfusion?

DR. KRANES: No; he did not.

DR. COPE: That is surprising because the difference in levels is out of the range of the error of the laboratory. That rise suggests that something had happened. The classic change that produces a rise in hemoglobin is a burn that is associated with increased capillary permeability, with loss of plasma and retention of the cells. This man, who had an infection

and was receiving chemotherapy, responded to the therapy and had a rise in red-cell count or hemoglobin mass. The patient with an infection generally loses red cells. I shall pass it over, for I do not see where it fits. If the patient had an internal hemorrhage, he ought to have had a drop and not a rise in hemoglobin.

How large was that abscess?

DR. GRANT V. RODKEY: There was an area of rather shapeless granulation tissue with a core that remained at the site of the previous biopsy and measured about 1.5 cm. in diameter. It was not a deep ulcer.

DR. COPE: This was not a rectal abscess, a gravitation abscess or a retroperitoneal infection that had descended and pointed retroperitoneally in front of the rectum or burst out in the rectum?

DR. RODKEY: No; it was adjacent to the prostate and slightly above it.

DR. COPE: There is evidence that it was a localized abscess, then.

DR. RODKEY: That interpretation was made at the time of operation, but we were not sure of it.

DR. COPE: The pancreas was not mentioned.

DR. RODKEY: The pancreas was carefully observed and was normal.

DR. COPE: I suppose it was unfair to ask about the pancreas so definitely because one of the diagnoses that I have in mind is acute pancreatitis. I was trying to tie together the symptoms in the upper abdomen and the masses in the rectum. Occasionally with pancreatitis there is a breakdown of the pancreas, with the formation of a retroperitoneal abscess, which may point in the groin or retroperitoneally in the bottom of the abdomen. The finding of a normal pancreas at operation excludes pancreatitis as the origin of the trouble.

There was clear-cut evidence that the patient had stones not only in the gall bladder but also in the common duct, but in the surgeon's opinion they were not associated with an acute inflammatory process. I gather that he did not believe that the stones accounted for the symptoms. This history, then, has been given me to indicate that I go on to something else. I suppose the exploration was sufficient to exclude a retroperitoneal abscess since the aorta was described as normal. Is that correct?

DR. RODKEY: That is correct.

DR. COPE: Dr. Castleman, two or three things about the death are very important. I wonder whether the physician who saw the patient at the time of the terminal episode would amplify it. Specifically, I want to be sure that the trachea was deviated to the left.

DR. CASTLEMAN: Dr. Jackson, can you answer that?

DR. B. B. JACKSON: I saw the patient right after the onset of the symptoms; the trachea was deviated to the left. This was confirmed by the anesthetist when he came over to carry out the bronchoscopy.

DR. COPE: I should have expected deviation to the opposite side. I assume that previously it was not deviated to the left and that on physical examination there was no deviation.

DR. JACKSON: I am sorry to have to report that I do not know where the trachea was before operation. I had not seen the patient before this episode.

DR. COPE: The x-ray films show it to be in the mid-line.

DR. HANELIN: That is correct.

DR. COPE: This terminal episode was definitely severe pain?

DR. JACKSON: When I saw the patient, he was comatose. He was not complaining of pain, and he was in the terminal episode.

DR. COPE: I am sure Dr. Jackson knows whether veins are dilated or not! They were flat?

DR. JACKSON: Yes, sir.

DR. COPE: Firstly, something happened during the terminal episode that caused severe pain or exacerbation of pain; secondly, the trachea moved to the left, with a shift of the mediastinum; and, thirdly, there was no congestion in the veins above the heart — the sign so characteristic of an embolus that is plugging the pulmonary arteries.

I shall now discuss the conditions that I have considered. It is obvious that this man had rectal symptoms and bleeding, and there were findings in the physical examination to go with those symptoms. He also had the onset of pain, the major complaint, with exertion and no previous history of coronary-artery disease. Moreover, the electrocardiogram gave excellent evidence against cardiac accident of the commonest type. I shall exclude coronary occlusion on the evidence and also pulmonary embolism on the basis of the description of the terminal episode, principally the absence of dilated neck veins and the displacement of the mediastinum.

One thing, which I did not dwell on as we passed along, is the red cells, casts and the albumin in the urine. I cannot for the moment fit that into the picture of hypertensive disease in a sick patient with fever, and I pass it by.

I am still concerned about a lung abscess, which may have ruptured terminally, but Dr. Hanelin saw none in the roentgenogram and I cannot imagine that one developed between the time the roentgenogram was taken and death.

I therefore come to the most likely diagnosis — that is, a dissecting aneurysm of the descending thoracic aorta. Dr. Hanelin tells us of an enlarged, fuzzy aorta. The original leakage could have occurred during physical exertion. The symptoms are consistent with that. The terminal findings, including the deviation of the trachea, can be explained by final rupture into the lower thorax. The dissecting aneurysm, which started three days before admission,

may have leaked slowly, causing pain, not always in the same place, a little more to the left as the dissection developed, according to Dr. Kranes, and finally ruptured.

I have also excluded a posterior retroperitoneal abscess, but believe there was a perirectal abscess. I suppose that must have been the cause of the fever. The septic process, I assume, responded to the chemotherapy. It is possible, however, that the abscess contributed in other ways. If there is a large blood clot anywhere in the body and an infection such as a sore throat or an abscess around a polyp or hemorrhoid develops elsewhere, there may be a metastasis of the infection to the blood clot. Beyond that I should not suppose that the rectal condition had contributed to death.

I therefore come to the diagnosis of dissecting aneurysm of the lower portion of the thoracic aorta, with chronic leakage and finally rupture and possibly with sepsis secondary to a perirectal abscess.

DR. CASTLEMAN: Dr. Kranes, have you anything to add about the clinical course?

DR. KRANES: I have often spoken to students and house officers about the danger of making too positive a diagnosis. What it does, of course, is to close one's mind and stop additional reflection on the problem. Yet I am forced to confess, with considerable chagrin, that a very short time after examining the patient I was quite certain he had two diseases: one was carcinoma of the rectum, and the second was acute cholecystitis. The problem as it then appeared was not so much a diagnostic as a therapeutic one — which operation to do first. If the acute right-upper-quadrant symptoms were to continue, it was quite natural to postpone the rectal operation since our hands would be forced, in operating on the gall bladder, either to remove or to drain it. But when the right-upper-quadrant symptoms subsided and the pain shifted to the left side of the abdomen, our attention was directed toward the rectal lesion. When Dr. Glenn E. Behringer carried out a proctoscopy and removed what was reported to be a rectal polyp, I was certain that he had missed the malignant base of the lesion, which felt hard and indurated, and seemed to extend about a quarter of the distance around the circumference of the rectum. Two days later in the operating room, however, nothing except what was reported in the record was found so Dr. Claude E. Welch operated on the gall bladder as described.

DR. CASTLEMAN: Dr. McKittrick, have you any comment?

DR. LELAND S. MCKITTRICK: I think Dr. Cope has done a splendid job. As a matter of fact he helped me to make the same diagnosis.

DR. CASTLEMAN: Dr. Bauer, have you any suggestions?

DR. WALTER BAUER: I, too, will make a diagnosis of dissecting aneurysm. I think it explains best what took place initially and could, of course, explain the albuminuria and hematuria in consequence of partial occlusion of one or both renal arteries or perhaps complete occlusion of one. I wonder whether the terminal episode was caused by rupture of the aneurysm into the pericardium, thereby explaining the pressure on the bronchus and the resulting changes observed on examination of the left side of the chest. With partial or complete collapse of the left lung the trachea should be displaced to the left.

DR. CASTLEMAN: I shall ask Dr. Warren and Dr. Abrams at the Statler if there are any questions.

DR. ARCHIE A. ABRAMS: It seems that early in the discussion, Dr. Merrill C. Sosman quickly sent up a note with the diagnosis, which is in full accord with the one given by Dr. Cope — namely, rupture of dissecting aneurysm of the descending aorta, with blockage of the left bronchus.

DR. COPE: That is a great comfort. That is a better explanation, it seems to me, than Dr. Bauer's. I cannot see how the blood could have entered the pericardium. When he was discussing it, I thought that perhaps he was suggesting a rupture of the heart. I was unable to explain why the mediastinum shifted; with a mass of collecting blood, the mediastinum should have been shifted to the opposite side.

CLINICAL DIAGNOSES

Cholecystitis and cholelithiasis.
?Carcinoma of rectum.

DR. OLIVER COPE'S DIAGNOSIS

Ruptured dissecting aneurysm of descending thoracic aorta.

ANATOMICAL DIAGNOSIS

Dissecting aneurysm of descending aorta, with rupture into left pleural cavity and lesser omental sac.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: When the abdomen was opened we found in the left upper portion a large amount of blood that seemed to surround the pancreas and left adrenal gland. At first glance, one might suspect that the patient had an acute hemorrhagic pancreatitis; however, there was no evidence of fat necrosis. On further extension of the incision to the chest, it was obvious that the hemorrhage that was seen in the abdomen had extended down through the diaphragm from the left side of the chest. The left side of the chest contained almost 2 liters of blood — some fresh, and some recently clotted. The source of this hemorrhage, as Dr. Cope predicted almost to the exact location, was a dissecting aneurysm of the aorta that began just below the left subclavian artery and had dissected downward into the abdomen to a point just above the left renal artery. The dotted line on

the diagram shows the extent of the medial hematoma as the result of the dissection (Fig. 3). It did not involve the mouths of either renal artery. It did surround or point to the mouth of the celiac artery. Perhaps if the patient had lived longer, it would have compromised the orifice of the celiac artery and produced gangrene of the bowel. There were three tears

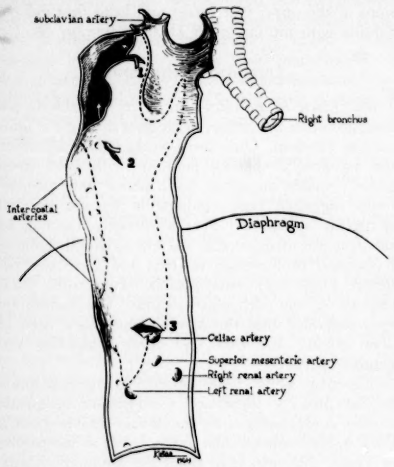

FIGURE 3.

in the dissecting aneurysm. The initial intimal tear (No. 1 on Fig. 3), I believe, occurred three days before admission. Then, as the dissection progressed downward in the media, the pressure in the medial hematoma gradually built up and probably led to the other two intimal tears (No. 2 and 3 on Fig. 3). Two days after the operation, there was an adventitial blowout in the region of the upper portion of the descending thoracic aorta. I think the pain during the period before the final external rupture was due not to leakage but to the dissection itself, because there was no evidence of external tear before the final episode.

We were able to find only a little chronic inflammation in the site of the adenomatous polyp that was removed; there was no evidence of carcinoma.

DR. RODKEY: One comment might be made. Dr. Welch considered the possibility of dissecting aneurysm. At operation, so far as he was able to tell by palpation of the aorta from a level above the pancreas down to the iliac arteries, it was within normal limits over this distance.

DR. KRANES: What did the trachea show?

DR. CASTLEMAN: I do not know; we have no note of whether it was deviated or not at the time of autopsy. Apparently, we did not look for it. I do not see how it could have been deviated to the left because there was a massive hemorrhage in the left pleural cavity, which was against the trachea. It should have been deviated to the other side. Are you sure, Dr. Jackson, that it was deviated?

DR. JACKSON: I am positive about it. I was eager to have this observation checked so I asked the physician from the Anesthesia Service to confirm this physical finding before he carried out the bronchoscopy.

CASE 42072

PRESENTATION OF CASE

A seventy-two-year-old man was admitted to the hospital because of jaundice.

Seven months previously, because of exertional dyspnea, wheezing and cardiac enlargement with atrial fibrillation, he was placed on a cardiac regimen, with relief of symptoms. The liver edge was felt 2 or 3 cm. below the right costal margin. The blood pressure was 140 systolic, 85 diastolic. During a routine examination two months before entry the liver edge was palpable 8 cm. below the right costal margin. The spleen was not felt; there was no ascites, and a stool guaiac test was negative. The serum bilirubin was 0.6 mg. per 100 ml., and the alkaline phosphatase 9.5 units. The bromsulfalein retention was 16 per cent. A month before admission he noted the onset of weakness. A week later deepening jaundice, unassociated with pain, and light-colored stools were noted. There had been a 15-pound weight loss during the seven months before entry. A history of heavy wine drinking was obtained from the family.

There was a past history of paresthesias of the feet during winter and an episode of transient loss of vision. He had had a spinal injury in childhood.

Physical examination showed a malnourished, deeply jaundiced, weak man with palmar erythema and multiple spider angiomas over the face and shoulders. There was no lymphadenopathy. The neck veins were flat when the patient was raised 45°. The left border of cardiac dullness extended to the anterior axillary line. The apical rate was 84 and irregular. The chest was emphysematous, with poor diaphragmatic motion. There was thoracic lordosis and lumbar kyphosis. Examination of the abdomen revealed distention and shifting dullness. The liver edge, which was firm and nontender, was palpable 8 cm. below the right costal margin. The spleen was not felt. The testes were atrophic. There was + edema of the legs. Rectal examination was negative.

The temperature was 97.6°F., the pulse 80 and irregular, and the respirations 20. The blood pressure was 100 systolic, 60 diastolic.

The urine gave a ++++ test for bile; the sediment contained an occasional white cell and granular

and hyaline casts per high-power field. Examination of the blood revealed a hemoglobin of 11.8 gm. per 100 ml. and a white-cell count of 8200. The serum nonprotein nitrogen was 29 mg., the total protein 5.9 gm., the albumin 2.9 gm., the globulin 3 gm., and the fasting blood sugar 100 mg., the serum bilirubin 19.6 mg. direct and 31.2 mg. total, the total cholesterol 235 mg., and the cholesterol esters 65 mg. per 100 ml., and the alkaline phosphatase 7.5 units. Cephalin flocculation was ++++ in forty-eight hours. Serum cholinesterase activity was 0.28 delta pH units per hour. Thymol turbidity was 8.6 units, and flocculation was +. The prothrombin content was 16 per cent. The blood Hinton test was negative. A stool specimen was grayish tan and gave a ++ guaiac test. An upper gastrointestinal series showed minimal increase in prominence of the gastric mucosal folds and elongation and slight mucosal irregularity of the duodenal cap and the first portion of the duodenum. There appeared to be an extrinsic pressure defect on this portion of the duodenum and a small calcification in this area. The duodenal loop was elongated transversely. There was a suggestion of a slight defect in the region of the ampulla of Vater (Fig. 1.).

FIGURE 1. *Spot Film of the Duodenal Loop, Showing an Area of Extrinsic Pressure upon Its Medial Aspect (Arrows).*

Abdominal paracentesis yielded 50 ml. of clear, yellow fluid on which the cytologic examination was unsatisfactory because no cells were seen; the total protein was 1.8 gm. per 100 ml.

The patient continued to be weak and at times was mildly disoriented. The abdomen became tense because of massive ascites. The blood ammonia on the ninth hospital day was 200 microgm. per 100 ml. The disorientation became worse, and by the eleventh hospital day he responded only to painful stimuli. A bilateral plantar extensor reflex was elicited. In spite of intravenous administration of glutamate the blood ammonia rose to 777 microgm. per 100 ml., and he became deeply comatose and died on the thirteenth hospital day. Terminally, there were clonic convulsions of the upper extremities and head that did not subside with intramuscular Dilantin therapy.

DIFFERENTIAL DIAGNOSIS

DR. JOHN A. BENSON, JR.*: In this elderly patient attention was drawn to the liver during a routine cardiac checkup. Only three weeks before admission did painless, deepening jaundice with light stools begin. Spider angiomas, liver palms and atrophic testes suggested poor conjugation by the liver of estrogenic substances. Poor synthesis of protein by the liver was manifested by the low albumin, cholinesterase and prothrombin activity, and there was deficient cholesterol esterification. Diagnostic paracentesis was not particularly helpful. The flocculation tests suggested that the albumin may have been of poor quality and that the elevated globulin was gamma in type.

The x-ray films are important. In the description in the protocol there are a suggestion of gastric varices, compression of the duodenum from without, a stone in the common duct and a defect at the papilla of Vater. I wonder, too, about the size of the spleen.

DR. STANLEY M. WYMAN: I do not believe that I can answer all the questions, Dr. Benson. There are no films to determine the size of the spleen. The question of varices in the stomach in the region of the cardia certainly exists. There is prominence of the rugae in the stomach in this region, but I do not have films of the lower esophagus taken with the intention of showing varices. The stomach otherwise seems grossly normal. The duodenal cap is elongated and perhaps pressed upon by the enlarged liver. The duodenal loop itself is not increased in size but reveals a suggestion of pressure at the junction of the second and third portions. That is by no means a definite finding; I think that, in a man who was critically ill and suffering from ascites, it may have been difficult to perform an ideal examination of this region. All I can say is that I am highly suspicious of an extrinsic lesion pressing on the duodenal loop, on its medial aspect, at the junction of the second and third portions (Fig. 1). The question of calcification adjacent to that region has been raised. I do not know exactly to which calcification the examiner referred. There are very thin streaks, which I take to represent calcified aorta, and a tiny, round calcification lying higher, which perhaps lies in the region of the gall bladder. I do not believe that the

*Assistant in medicine, Massachusetts General Hospital.

small calcification described was connected with the possible defect in the medial portion of the duodenum.

DR. BENSON: Do the x-ray films of the chest taken earlier demonstrate sufficient clearing so that you would not be concerned about lymphatic spread of carcinoma?

DR. WYMAN: Two examinations, one about seven months before death and the other six weeks later, show prominence of the hilar shadows, which I think becomes less marked in the later examination. I should take this change to mean improvement of congestive heart failure. There is still some pulmonary congestion, but I think that metastatic carcinoma is quite unlikely.

DR. BENSON: Finally, ascites increased, and coma rapidly ensued. There was no obvious infection, paracentesis, hemorrhage or alcoholic spree that I know of to precipitate the coma. One wonders whether the ++ guaiac test on the stool on admission heralded a gastrointestinal hemorrhage as a source for the increased blood ammonia. The failure, however, of glutamate to reduce the exceedingly high blood ammonia suggests an endogenous source of ammonia. Yet it must be remembered that one third of the patients with so-called acute exogenous encephalopathy described by McDermott and his associates* died despite such therapy, so that this is not a good differential point. The high blood ammonia does suggest that a large portacaval shunt existed undetected, with a reduced hepatic blood flow.

There can be little doubt that there was severe parenchymal liver damage. The hepatomegaly, liver-function tests and cholemic death all support this. The patient was chronically ill, and I believe he had cirrhosis. A superimposed viral hepatitis could have been the factor precipitating coma, but the history lacks appropriate symptoms. The patient's wine-drinking background does not sway me in the diagnosis of the type of cirrhosis. I do not believe that cardiac cirrhosis was present. The size of the liver increased in spite of a successful cardiac regimen; the neck veins were not distended; there were no murmurs of mitral or tricuspid stenosis, and the cardiac silhouette did not suggest either of these or constrictive pericarditis. Nevertheless, there was atrial fibrillation. Jaundice can occur in cardiac failure as a result of severe central necrosis of the liver without pulmonary infarction, pulmonary edema or full neck veins. There seems to me to be too great a disproportion between the apparently mild cardiac problem and the severe liver disease for the former to have caused the latter. Hemochromatosis, another possible etiology of portal cirrhosis, deserves mention because of the mild cardiac disease, which is not uncommon in this condition. Furthermore, hepatoma is twice as common in this type of portal cirrhosis. But there was no reported pigmentation, diabetes or increased liver density on x-ray examination, and the age and anemia would be a bit unusual for this disease.

Although cirrhosis could explain most of the picture, I believe that there was an associated factor. The problem is to determine that, without adding too many diagnoses; I shall discuss obstruction, a vascular phenomenon and tumor.

The x-ray films make me lean toward obstruction of the common bile duct. The deformity in the region of the papilla of Vater suggests either a tumor or a nonradiopaque stone in the lower common duct. The symptoms were limited to progressive jaundice and nonremittent light-colored stools. The earliest chemical determinations before jaundice developed suggest interference with phosphatase and bromsulfalein excretion. The later bilirubin of 31 mg. and the cholesterol of 235 mg. per 100 ml. are rather high for uncomplicated parenchymal damage. To decide for tumor rather than stone as the cause of the obstruction is not easy in the face of the x-ray calcification in the region of the duodenum. But the melena, the lack of evidence for cholangitis (the patient did not have fever and chills), the absence of calcification at the ampulla of Vater and the unremitting jaundice make me favor tumor. More important, the enormous size of the liver, together with the lack of splenomegaly in a man that ill from parenchymal disease, indicates massive involvement of the liver by metastases. Cancer at the papilla of Vater, in the pancreas or in the bile duct is a possible primary lesion. I suspect that the clinicians handling the patient wanted to perform a needle biopsy of the liver but did not because of the low prothrombin activity and the impression that any information obtained would have been too late to help him. One last point about gallstones: silent calculi are sometimes associated with cancer of the bile ducts; the calcification noted in the x-ray film may have represented a common-duct stone. Scarring of the gall bladder accompanying a stone or the large size of the liver may explain why the gall bladder was not felt. I do not believe gallstones were responsible directly for the biliary obstruction.

When ascites rapidly becomes severe, portal-vein thrombosis must be considered. It occurs in about 10 per cent of cirrhotic patients. But splenomegaly, bleeding varices, pain, fever and collateral vessels in the abdominal wall — all rather crucial to this diagnosis — were missing. Another vascular phenomenon that might have precipitated the patient's rapid death is thrombosis of the hepatic veins, or the Budd–Chiari syndrome, secondary to cirrhotic or neoplastic changes in the liver. Here, again, pain and abdominal collateral vessels might have been expected.

Finally, hepatoma complicating cirrhosis could have been the cause for the terminal events. It is difficult to exclude this tumor, but I do not believe

*McDermott, W. V., Jr., Wareham, J., and Riddell, A. G. Treatment of "hepatic coma" with l-glutamic acid. *New Eng. J. Med.* **253**: 1093-1102, 1955.

it satisfactorily explains what I have interpreted as an obstructive picture. Also, there was no pain. Of course, the patient may have been too confused to give an accurate history or may have had the high pain threshold of old age.

I believe that there was cirrhosis, possibly of the postnecrotic variety, with considerable venous obstruction producing ascites. There was probably a large portacaval shunt, possibly through gastric varices. Superimposed was metastatic carcinoma. I believe that this primary carcinoma was in the lower biliary tree and caused common-duct obstruction. Statistically, carcinoma, spreading from the body to the head of the pancreas, is the commonest. The filling defect at the ampulla of Vater may have been caused by an obstructing lymph node involved in such a carcinoma. Cancer of the papilla of Vater or the distal bile duct is a close second choice, but these types are only about a fourth as common. There was probably a bile nephrosis, with bile casts and hydropic changes in the proximal convoluted tubules, to which terminal therapy with hypertonic glucose infusions may have contributed. Finally, there was probably coronary-artery disease, with cardiac enlargement and atrial fibrillation.

DR. ROBERT E. SCULLY: Dr. Point, you saw this patient on the ward.

DR. WARREN POINT: I did see him for the very purpose that Dr. Benson mentioned: the question of liver biopsy. When I saw him he was moribund so that it was perfectly obvious that liver biopsy would have contributed nothing toward helping him. Moreover, the prothrombin content, anemia and so forth all prohibited such a procedure. My opinion was the same as Dr. Benson's: that the patient probably had cirrhosis, although I was suspicious of an ordinary portal cirrhosis or Laënnec's cirrhosis. I also thought, as I recall, that there was probably a superimposed carcinomatous process in the liver, either primary hepatoma or secondary to carcinoma of the pancreas. Now I should bet on hepatoma.

CLINICAL DIAGNOSIS

?Carcinoma of pancreas or ampulla of Vater, with biliary obstruction and metastases to liver.

DR. JOHN A. BENSON, JR.'S, DIAGNOSES

Cirrhosis of liver, postnecrotic type.
Carcinoma of body and head of pancreas, with obstruction of common bile duct and metastases to liver.
Ascites.
Bile nephrosis.
Coronary-artery disease.

ANATOMICAL DIAGNOSES

Cirrhosis of liver, Laënnec's type.
Hepatoma, with metastases to lymph nodes causing extrinsic pressure on common bile and hepatic ducts.
Ascites.
Cholecystitis, chronic.
Hydrops of gall bladder.
Cholelithiasis.
Coronary-artery disease.
Pulmonary emphysema.

PATHOLOGICAL DISCUSSION

DR. SCULLY: At autopsy the abdominal cavity contained 1 liter of cloudy yellow fluid. The liver was 4 cm. below the costal margin in the right midclavicular line, was cirrhotic and was diffusely bile stained. The lateral half of the right lobe was completely replaced by firm, white neoplasm. There was no obvious invasion of the venous system of the liver by tumor. The gall bladder was filled with clear, yellow fluid and had a thickened wall. In the cystic duct, just at its origin, was an impacted calculus 5 mm. in diameter. The region of the ampulla of Vater appeared normal, but the common bile duct was markedly compressed by lymph nodes enlarged by metastatic tumor. The pancreas was normal. Microscopically, the cirrhosis was of Laënnec's or the nutritional type. All the cirrhotic nodules showed severe bile stasis secondary to the obstruction of the common bile duct. The tumor in the liver and lymph nodes was a classic hepatoma. The spleen was at the upper limits of normal in size. There were small esophageal varices, evident only on microscopical examination.

The heart was slightly enlarged, and there was a moderate amount of coronary-artery disease but not as much as we had expected in view of the cardiac failure. The lungs showed a moderate amount of emphysema. The kidneys showed bile staining, but were otherwise unremarkable.

DR. POINT: Once again it has been shown that the alkaline phosphatase is not specific for carcinoma of the liver. Many physicians think that there must be a moderately high alkaline phosphatase for one to make that diagnosis, but such a conclusion is unwarranted.

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PRISON CAMPS — DEAD LINE IN NUTRITION

AT Andersonville, which is in the news again after eighty years,[1] at Buchenwald and at the prison camps of North Korea a dead line in malnutrition has been repeatedly demonstrated. Thus, of the North Korean campaign, 5 physicians[2] who had been prisoners could write:

> By the spring of 1951 the deaths in the communist prisoner of war camps were caused directly or indirectly by starvation, exposure and by the harrassment of the enemy. . . . During the first month or two of captivity most of the deaths occurred among the wounded. . . . After the first five or six months of captivity the majority of deaths occurred among persons suffering from pellagra or beriberi.

Some idea of the diet may be appreciated from the Thanksgiving meal of 1950: for each man a millet-ball weighing less than 200 gm. and soup prepared by boiling in water 9 heads of cabbage per 500 men.

Deficiency disease and death by the harrassment of the enemy was, of course, also the experience encountered at Buchenwald, Belsen and Dachau a few years earlier and many years earlier in the Civil War camps, especially toward the end of that war. Doubtless untold millions have languished to death in the course of centuries of fighting.

To physicians accustomed to thinking of prison miseries solely as purposeful atrocities of the enemy it may be more profitable to contemplate the matter with an eye to prevention than to dwell descriptively on a tortured phenomenon that is as old as captivity. That has been done recently in a fictionalized account put together from the stories of survivors of Andersonville,[1] many of whom contributed the first-hand tales of the 85 references. Perhaps the most articulate of these was an Illinois private, J. P. McElroy, who was captured late in 1863 but managed to survive incarceration at Libby, Andersonville and Florence. At Andersonville, where the staple diet was "rusty bacon and coarse maggot-filled bread," scurvy was the particular hazard, usually manifested first in the mouth:

> The breath became unbearably fetid; the gums swelled until they protruded, livid and disgusting, beyond the lips. . . . In attempting to bite the hard corn bread furnished by the bakery the teeth often stuck fast and were pulled out. The gums had a fashion of breaking away in large chunks, which would be swallowed or spit out.

At Florence the diet was practically nothing but a brick of corn bread, with no animal protein of any kind. Here the consequences were clearly those of pellagra:

> The faculties shrank under disuse and misfortune, until they forgot their regiments, companies, places and date of capture, and finally, even their names. I should think that by the middle of January, at least one in every ten had sunk to this imbecile condition. It was not insanity so much as mental atrophy — not so much aberration of the mind, as a paralysis of mental action. The sufferers became apathetic idiots, with no desire or wish

to do or be anything. If they walked around at all they had to be watched closely, to prevent their straying over the Dead Line, and giving the young brats of guards the coveted opportunity of killing them.

Scurvy, beriberi, pellagra and low protein intake — kwashiorkor, as it is fashionably called today — are among the "occupational hazards" and Dead Lines of the PW, especially in a totalitarian state and especially if capture occurs during the losing phases of any war. Today, of course, there is also brain washing, which, however, is not altogether a new concept. Kantor brings this out in his version of the tactics of Captain Henry Wirtz, who was the counterpart of the Beast of Belsen at Andersonville — and was promptly executed after the last battle had been won.

Within the confines of the various dead lines that marked the boundaries beyond which men were shot, the PW's of 1864, 1944 and 1951 were kept on diets like guinea pigs, eating rolled oats. They were not knowingly starved to death, although as McElroy made clear in his time and Anderson and his colleagues[2] eighty years later, there was "no uniform desire to keep prisoners alive" — a masterpiece of understatement. However, when mass slaughter was adopted as high policy whole communities were burned, gassed or simply shot. To such depths men have degenerated, and probably more frequently than has ever been known.

The one constructive thing that might be done by people powerless to influence an enemy's motivation would be to give their own foot soldiers a few hours' indoctrination on nutrition and survival on land similar to that given pilots who may be forced down at sea.

It is largely ignorance of basic dietary facts that made both victor and vanquished pay such grisly prices for the doubtful success of capturing each other's troops in battle. And yet one small yeast cake and some dandelion seed would have sufficed to maintain the general health of many who died. The cells of a single yeast cake might be cultured into a never-ending supply of vitamin B components, and the leaves of the lowly dandelion made into a tea to supply vitamin C in abundance.

References

1. Kantor, M. *Andersonville*. 767 pp. Cleveland & New York: World Publishing Co., 1955.
2. Anderson, C. L., Boysen, A. M., Esensten, S., Lam, G. N., and Shadish, W. R. Medical experiences in Communist POW camps in Korea. *J.A.M.A.* **156**:120-122, 1954.

"CAPTAIN STAPHYLOCOCCUS"

JOHN Bunyan once referred to consumption as "Captain of the Men of Death," and indeed, for many years, and in many parts of the world, tuberculosis led all other infectious diseases as a cause of death. During the first quarter of this century, however, according to Osler, pneumonia took over this title, having become the most widespread and fatal of all acute conditions.

At present tuberculosis is being reasonably well controlled by specific chemotherapy and other supportive measures. Pneumonia, or at least pneumococcal pneumonia, the most common form that was responsible for the high mortality in the past, also is no longer a cause for concern, since that disease responds promptly and decisively to any of a number of available antimicrobial agents.

Evidence is now accumulating that, at least so far as hospitalized patients are concerned, top place as a cause of death has rapidly passed to the staphylococcal infections. A recent report to this effect comes from the Montreal General Hospital, where de Vries and Pritchard* have been making cultures routinely of heart's blood, cut surfaces of lungs and other infected areas of all patients coming to autopsy. In a series of 213 such cases observed from October, 1953, to May, 1954, these cultures yielded *Micrococcus pyogenes* in 87 cases, *Diplococcus pneumoniae* in 4, *Klebsiella pneumoniae* in 3 and *Streptococcus pyogenes* in 1. All but 7 of the 87 staphylococcal strains were obtained from the heart's blood or lungs or both.

These results are most striking in view of the fact that in 311 autopsies done at the same hospital in 1950, the records showed only 3 cases of bronchopneumonia and 2 of septicemia due to staphylococci, but cultures were not done routinely during that period. In the recent cases, almost all the staphylococcal infections were considered to be secondary and terminal events in the course of obvious debilitating diseases; only 3 were from patients who were admitted to the hospital with a diagnosis of staphylococcal septicemia.

Another interesting feature of this study was the indication that most of these infections had probably been acquired in the hospital. The majority of the strains (61 per cent) belonged to phage Group 3, which is also the most common group among staphylococci found in carriers in hospital personnel. Moreover, as in other hospitals, all but a small proportion of the staphylococcal strains in the autopsied cases were resistant to penicillin, and about half were also resistant to the tetracyclines.

There is now an intensive search for antibiotics that are specifically and highly active against staphylococci. If successful, this may, of course, help solve the problem, provided that the infections are recognized and treated early. In the event that the battle against the staphylococcus is won by such means or by other methods, can another group of infectious agents—perhaps the enteric organisms or some viruses —be expected to take over? The answer may not be long in coming. Meanwhile, hospitals are confronted with large and increasing numbers of serious staphylococcal infections that are resistant to available therapy and are taking a considerable toll in lives and in debilitating illnesses.

*de Vries, J. A., and Pritchard, J. E. Increase in serious staphylococcal infections as shown by post-mortem investigations. *Canad. M. A. J.* **73**:827, 1955.

SUNT LACRIMAE

ACCORDING to the Acts of 1921, Chapter 181 of the Great and General Court of the Commonwealth of Massachusetts, comprising Article XII of the constitution of the Massachusetts Medical Society, the Society is authorized to publish and distribute a "journal or periodical to be devoted mainly to medical and surgical science." Under this authorization the venerable *Boston Medical and Surgical Journal* was purchased by the Society thirty-five years ago and since that time has been published by the Committee on Publications and sent (almost automatically) to all active fellows in good standing, whether resident or nonresident, and to senior fellows, free of all charge, on annual request.

This distribution of the *Journal,* however, — now the *New England Journal of Medicine* — has been based on the universal law of *quid pro quo.* Although not specifically mentioned in the Constitution, the *By-laws,* the Council Rules or the Code of Ethics of the Massachusetts Medical Society, a statute of limitations was early invoked for the sending of the publications of the Committee, *inter alia, in futuro* and *ceteris paribus,* to those fellows who had failed to discharge their fiscal obligation to the Society by March 1 of any year, the assessment having been due January 1.

The editors of the *Journal,* reluctant to impose so severe a penalty, have on their own responsibility added a period of grace extending to the Ides of March or beyond before removing the recalcitrant fellow from the mailing list, but after the extended date cash only counts, nor can the journals that have been omitted be supplied; the number printed each week is based on the number of bona fide subscribers.

Thus in 1955, 1040 fellows were deprived of the ecstasy of receiving their journals; in 1954, 1002 awaited without reward the postman's ring, and in 1953 this special life line to 843 fellows was cut. The hour approaches; *sunt lacrimae rerum.*

ARTHRITIS CLINIC

ELSEWHERE in this issue of the *Journal* The Robert Breck Brigham Hospital announces the establishment and the opening, on February 1, of an outpatient clinic for the diagnosis and treatment of the arthritis problems of adult and child alike. The clinic, where no professional charge is made, is separate from the consultation clinic in which referred private patients are seen on a fee-for-service basis.

The Robert B. Brigham Hospital, chartered under the will of its founder in 1903 and opened on the medical acropolis of Parker Hill in 1914, was originally designed simply as a hospital for patients with chronic disease and there many a student of a former generation had his introduction, not only to the arthritides, unsalvaged and unsalvageable, but to the barrel chests of chronic emphysema and to helpless and hopeless patients with progressive carditis.

This picture has changed, and the Robert Brigham, consolidating its efforts on the study and treatment of rheumatic diseases, has become unique in the country for its concentration in this particular field. As a teaching center in arthritis and orthopedic surgery it is allied with the medical schools of Harvard, Boston and Tufts universities; it serves also as a center of instruction in physical therapy for Boston University and Tufts, in social work for Simmons College, and in occupational therapy for the University of New Hampshire and the Boston School of Occupational Therapy. In addition research projects are under way to a total of $75,000 in the last three years alone.

PRIZE-ESSAY COMPETITION

The $100 prize-essay competition for fourth-year students closes March 1, 1956.

Full details were published in the *Journal* of October 27, 1955.

Female Physicians Two Hundred Years Ago. — *We read in reference to a subject with which the present time is not unfamiliar: — 'Ordered, that Jane Hawkins has liberty till the beginning of the third month, called May, and then the Magistrate, if she does not depart before, is to dispose of her; and in the meantime she is not to meddle in surgery or physic, drugs, plasters or oils, nor to question matters of religion except with the ministers for her own satisfaction.'*

Boston M. & S. J., *February 21, 1856*

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

This year the Committee on Finance has voted to distribute $6,000 to the district societies toward defraying their operating expenses from the surplus in the General Fund at the end of 1955.

Members are reminded that the percentage of this sum that is allocated to their own district is determined by the number of dues from that district paid by March 1, 1956. Members who have not paid their dues by this date are automatically removed from the mailing list of the *Journal* until such dues are paid.

ELIOT HUBBARD, JR.
Treasurer

DEATHS

GRIMES — Loring Grimes, M.D., of Swampscott, died on June 19, 1955. He was in his seventy-fifth year.

Dr. Grimes received his degree from Harvard Medical School in 1904. He was formerly president of Essex South District Medical Society, chairman of the Swampscott Board of Health, and chief of the surgical staff at Lynn Hospital.

He is survived by two sons and a daughter.

GUILD — Frederick W. Guild, M.D., of Grafton, died on September 30. He was in his seventy-first year.

Dr. Guild received his degree from University of Vermont College of Medicine in 1909. He was formerly associate medical examiner in the Fifth District and a member of the staffs of Milford and Hahnemann hospitals.

He is survived by his widow, a son and a daughter.

SANDS — Herman C. Sands, M.D., of Salem, died on December 6. He was in his fortieth year.

Dr. Sands received his degree from Middlesex University School of Medicine in 1942. He was a member of the American Academy of General Practice.

He is survived by his widow, a son and a daughter.

VOHR — Dorothy R. L. Vohr, M.D., of Lee, died on December 14. She was in her fiftieth year.

Dr. Vohr received her degree from Middlesex University School of Medicine in 1933. She was formerly medical officer at Harbor Hospital, Brooklyn, and a member of the board of Riggs Clinic.

She is survived by her mother, her husband, two sons and a daughter.

VROOMAN — Earle M. Vrooman, M.D., of North Adams, died on December 20. He was in his seventy-ninth year.

Dr. Vrooman received his degree from Baltimore Medical College in 1903.

He is survived by his widow, a son and a daughter.

CORRESPONDENCE

PHYSICIAN AND CITIZEN—JOHN P. PETERS, M.D.

To the Editor: When Dr. John P. Peters began the task of writing *Quantitative Clinical Chemistry* thirty years ago, the subject was barely adolescent. During the decade before his death on December 29, 1955, he had seen clinical chemistry arrive at full maturity, as an indispensable part of medicine, and in this growth he had played a major part. In fact it may be said that in his time he was the leading exponent of the conceptual framework upon which this development occurred: "The disorders encountered in disease may be regarded as normal physiologic responses to unusual conditions produced by pathologic processes." Yet this work represented but one facet, perhaps not the major one, in a many-sided scientific life.

First and foremost Dr. Peters was a physician, a man who took care of the sick. In this role he brought to bear on the problems of disordered physiology an extraordinary critical acumen that enabled him to foresee the nature of the disturbance and its proper therapy years before the persistent plodding of others established the truth of his insight. No symptom was too minor to escape his scrutiny of its mechanism or his perseverance in attempting to alleviate it. Probably few but his patients, and the small group of young physicians who each year struggled to keep up with his untiring energy, knew of his infinite pains or of his capacities in caring for the most minute details of illness. The attention to detail that characterized his care of his patients was also apparent in his scientific publications. One never found a loose thought or a loose statement in his work. If a minor detail could not adequately be documented from the literature, publication was delayed until the point could be settled in his own laboratory. Although he vigorously opposed the "apprentice" system of medical education, he was at his best in teaching the small group at the bedside or in the laboratory by example rather than by words. His students, now widely scattered in hospitals and medical schools throughout the world, continue to spread his philosophy of medicine — in practice, teaching and investigation. Few teachers have so definitely molded the future careers of their pupils as Dr. Peters.

Speaking at memorial services in New Haven, Professor Fowler Harper of the Yale Law School said, in part:

> There were two men named Peters — Peters the Scientist, Peters the Citizen. It is not easy to talk about Citizen Peters. He was, in a sense, a bundle of contradictions. He was a gentle and benign man. Yet he could be hard and stern. And if he spoke softly, it was not that he had little to say nor that he doubted his premises. And although he was a skeptic, he was not a cynic and he was unswerving in his consecration to his principles. Certainly he was a dedicated man — dedicated to science and to the truth as he saw it, and he saw it more clearly than most men.
>
> Dr. Peters was warm in his affection. He gave freely — to his family, to his friends, his students and his patients. But he was also a severe man, stubborn, at times cantankerous. On the other hand, he was tolerant — tolerant even of wicked men, although not of the evil in them. And if his tolerance sometimes failed, it was only at the intolerance and bigotry of others. Nor could he stand hypocrisy or sham in any form.
>
> It was William Lloyd Garrison who warned at the masthead of the first issue of The Liberator: "I will be as harsh as truth and as uncompromising as justice." Dr. Peters was that harsh and that uncompromising. Although by his scientific works, Dr. Peters wrote himself into the slender volume of the immortals, he easily attained a humility that lesser men seldom acquire.
>
> I knew Dr. Peters only in the later years but the relationship was one of the most rewarding experiences of my life. I think I saw with some clarity the many contradictions of his character — the kindliness and the steel, the simplicity and the urbanity, the intricate and the complicated personality, the precision-like mechanism of his mind, the softness and warmth, the flint-like quality of his courage. In man's long struggle to civilize himself, it would be hard to find better evidence of success. My affection for Dr. Peters was deep and abiding for many reasons. But I think it was his fearlessness that made me admire him most. In a world of frightened people, it was a refreshing and invigorating phenomenon.
>
> Dr. Peters was an individualist. He did not mind if he was in the minority as he frequently was. He did not mind if he was a minority of one. And yet, he felt strongly about the collective welfare and had definite ideas as to what should be done to promote it. Although his own patients received the best medical attention, he knew the American people as a whole did not have adequate medical care and he did everything in his power to improve it. To be sure, Dr. Peters was neither an infallible scientist nor was he the quintessence of all virtue. He was altogether human. But there are few men who have done more good things for more people with more modesty.

MAURICE B. STRAUSS, M.D.

Boston

BOOK REVIEW

Die Bronchographie. By Dr. Ernst Stutz and Dr. Heinz Vieten. 4°, cloth, 250 pp., with 181 illustrations. Stuttgart: Georg Thieme, 1955. DM 66.- $15.70. (72. *Ergänzundsband der Fortschritte auf dem Gebiete der Röntgenstrahlen vereinigt mit Röntgenpraxis; Vorzugspreis für Abonnenten der Zeitschrift,* DM 59.40. $14.15.) (Distributed by the Intercontinental Medical Book Corporation, New York City.)

This book is intended mainly for the use of the radiologist. After ample elaboration of the technic, with the addition of chapters on normal and pathologic anatomy and physiology of the bronchial system, the main body of the book contains a discussion of the morphologic changes in the different pathologic conditions. Concise introductions on pathology and symptomatology precede the sections on the single clinical units. The illustrative material is made up of 234 figures

in optimal reproduction; the research worker will be helped by a bibliography of 1654 items. In spite of several recent monographic presentations of the topic this authoritative and excellently published work will doubtless find its way to the desk of the roentgenologist for consultation and as a reference organ into general medical libraries.

GEORGE KELEMEN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Sports Injuries: Prevention and active treatment. By Christopher Woodward. 12°, cloth, 128 pp., with 57 illustrations. London: Max Parrish, 1954. $3.00. (Distributed in the United States by Track and Field News, Los Altos, California.)

Psychocutaneous Medicine. By Maximilian E. Obermayer, M.D., clinical professor of dermatology and chairman, Department of Dermatology, University of Southern California School of Medicine, and senior consultant in dermatology, Veterans Administration Hospital, Long Beach, California. 8°, cloth, 487 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1955. $9.75. (Publication No. 239, *American Lecture Series.*)

Bedside Diagnosis. By Charles Seward, M.D., F.R.C.P. (Edin.), physician, Royal Devon and Exeter Hospital, consulting physician, Princess Elizabeth Orthopaedic Hospital, West of England Eye Infirmary and Ministry of Pensions, and Honeyman Gillespie Lecturer. With a foreword by Sir Henry Cohen, M.D., D.Sc., LL.D., F.R.C.P., F.F.R., professor of medicine, University of Liverpool. Third edition. 12°, paper, 408 pp., London: E. & S. Livingstone, Limited, 1955. $4.00. (Distributed in the United States by Williams and Wilkins, Baltimore.)

Midwifery. By 10 teachers, under the direction of Frederick W. Roques, M.D., M. Chir., F.R.C.S., F.R.C.O.G. Edited by Frederick W. Roques, John Beattie, and Joseph Wrigley. Ninth edition. 8°, cloth, 607 pp., with 249 illustrations. London: Edward Arnold, Limited, 1955. $7.00. (Distributed in the United States by Williams and Wilkins, Baltimore.)

Biologie cellulaire. By Léon Hirth, assistant professor, Lycée Buffon; and Joseph Stolkowski, assistant professor, Lycée Buffon. 12°, paper, 408 pp., with 190 illustrations. Paris: Presses Universitaires de France, 1955. Francs 2,000.

Bakteriologie und Serologie: Ausgewählte Untersuchungsmethoden für das bakteriologische und serologische Laboratorium. By Dr. Lothar Hallmann, Hamburg. 8°, cloth, 850 pp., with 273 illustrations and 1 chart. Stuttgart: Georg Thieme, 1955. DM 58.50.- $13.90. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

La obstetricia in Venezuela: ensayo histórico. By Dr. Pedro A. Gutiérrez Alfaro, Ministro de Sanidad y Asistencia Social; and Ricardo Archila, chief physician, División de Unidades Sanitarias, and assistant professor, Cátedra de Historia de la Universidad Central. In collaboration with Dr. Oscar Agüero, chief of the clinic, Cátedra de Clínica Obstétrica de la Universidad Central; and J. Sahagún Torres, adjunct physician, División Materno Infantil. 8°, paper, 606 pp., with illustrations. Caracas: "Ragon", C.A., 1955.

First International Symposium on the Control of Insect Vectors of Disease. (Supplemento ai rendiconti, Dell'Istituto Superiore Di Sanita.) 8°, paper, 396 pp., with illustrations and tables. Rome: Fondazione Emanuele Paterno, 1954. (Distributed in the United States by Charles C Thomas, Springfield, Illinois.)

Survey of Clinical Pediatrics. By Lawrence B. Slobody, M.D., professor of pediatrics, New York Medical College, director of pediatrics, Flower and Fifth Avenue Hospitals and Metropolitan Hospital, and medical director, Children's Center, New York City. Second edition. 8°, cloth, 502 pp., with 2 illustrations and 27 tables. New York: Blakiston Division, McGraw-Hill Book Company, Incorporated, 1955. $9.50.

Anxiety and Stress: An interdisciplinary study of a life situation. By Harold Basowitz, Harold Persky, Sheldon J. Korchin and Roy R. Grinker, from the Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, Chicago. 8°, cloth, 320 pp., with 70 tables and charts. New York: Blakiston Division, McGraw-Hill Book Company, Incorporated, 1955. $8.00.

The Biologic Effects of Tobacco: With emphasis on the clinical and experimental aspects. Edited by Ernest L. Wynder, M.D., head, Section of Epidemiology, and associate, Sloan-Kettering Institute for Cancer Research. With a foreword by Joseph Garland, M.D., editor, *New England Journal of Medicine.* 8°, cloth, 215 pp., with 20 illustrations and 7 tables. Boston: Little, Brown and Company, 1955. $4.50.

Treatment in Psychiatry. By Askar Diethelm, M.D., professor of psychiatry, Cornell University Medical College, and psychiatrist-in-chief, New York Hospital (Payne Whitney Psychiatric Clinic). Third edition. 8°, cloth, 545 pp. Springfield, Illinois: Charles C Thomas, 1955. $9.50.

A Primer of Electrocardiography. By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University of Louisiana School of Medicine, physician-in-chief, Tulane Unit, Charity Hospital, consultant in cardiovascular diseases, Ochsner Clinic, Ochsner Foundation Hospital, Veterans Administration Hospital, visiting physician, Touro Infirmary, and consultant in medicine, Hôtel Dieu and Illinois Central Hospital, New Orleans; and Travis Winsor, M.D., assistant clinical professor of medicine, University of Southern California Medical School, director of Nash Cardiovascular Foundation, Hospital of the Good Samaritan, junior attending physician, Los Angeles County Hospital, and junior attending physician, Children's Hospital, Cardiac Department, Los Angeles. Third edition, thoroughly revised. 8°, cloth, 286 pp., with 281 illustrations and 7 tables. Philadelphia: Lea and Febiger, 1955. $5.00.

Breast Cancer: Its diagnosis and treatment. By Edward F. Lewison, M.D., assistant professor of surgery, Johns Hopkins University School of Medicine, surgeon, Johns Hopkins Hospital, and surgeon, Out-Patient Department, Breast Clinic, Division of Tumor Clinic, Johns Hopkins Hospital. 4°, cloth, 478 pp., with 181 illustrations and 92 tables. Baltimore: Williams and Wilkins, 1955. $15.00.

The Mayo Clinic. By Lucy Wilder. Second edition. 4°, cloth, 69 pp., with illustrations by Ruth Barney. Springfield, Illinois: Charles C Thomas, 1955. $3.75.

Poet and Psychiatrist: Merrill Moore, M.D.: A critical portrait with an appraisal of two hundred of his poems. By Henry W. Wells. 8°. cloth, 325 pp. New York: Twayne Publishers, 1955. $5.00.

Ciba Foundation Colloquia on Endocrinology: The human adrenal cortex. Vol. 8. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; and Margaret P. Cameron, M.A., A.B.L.S., assisted by Joan Etherington. 8°, cloth, 665 pp., with 227 illustrations and tables. Boston: Little, Brown and Company, 1955. $10.00.

Proctologic Anatomy. By R. V. Gorsch, M.D., F.I.C.S., F.A.P.S., D.A.B.P., clinical professor of proctology, New York Polyclinic Medical School and Hospital, director of proctology, Midtown Hospital, New York City, and consultant proctologist, Monmouth Memorial Hospital, Long Branch, New Jersey, and Department of Correction Hospitals, City of New York. Second edition. 8°, cloth, 310 pp., with 155 illustrations. Baltimore: Williams and Wilkins, 1955. $8.00.

Sexual Hygiene and Pathology: A manual for the physician. By John F. Oliven, M.D., psychiatrist, Vanderbilt Clinic, Columbia-Presbyterian Medical Center, New York City. 8°, cloth, 481 pp. Philadelphia: J. B. Lippincott Company, 1955. $10.00.

Artrite reumatóide. By Jacques Houli, assistant in clinical medicine, Faculcade Naçional de Medicina da Universidade do Brasil, chief, Secção de Reumatologia e Doenças Osseas da 5.ª Cadeira de Clínica Médica, reumatologista, Instituto de Aposentadorias e Pensoes dõs Industriários, and associate internist, Clínica Ortopédica do I.A.P.I., Médico Clínico do Ministério da Educação e Saúde, da Sociedade Brasileira de Reumatologia. 8°, paper, 264 pp., with 44 illustrations, 28 tables and 7 charts. Rio de Janeiro, 1953. $2.50.

Obstetrics. By J. P. Greenhill, M.D., senior attending obstetrician and gynecologist, Michael Reese Hospital, Chicago, obstetrician and gynecologist, Associate Staff, Chicago Lying-in Hospital, attending gynecologist, Cook County Hospital, Chicago, and professor of gynecology, Cook County Graduate School of Medicine. Eleventh edition. 4°, cloth, 1088 pp., with 1170 illustrations and 7 tables. Philadelphia: W. B. Saunders, 1955. $14.00.

Lehrbuch und Atlas der Anatomie des Menschen. Vol. 2. By Dr. Fr. Kopsch, professor of anatomy and director, Anatomisches Instituts der Humboldt-Universität Berlin. 4°, cloth, 768 pp., with 782 illustrations. Stuttgart: Georg Thieme, 1955. $15.35. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The Spine: A radiological text and atlas. By Bernard S. Epstein, M.D., chief, Department of Radiology, Long Island Jewish Hospital, New Hyde Park, New York. 4°, cloth, 539 pp., with 331 illustrations. Philadelphia: Lea and Febiger, 1955. $16.50.

Diseases of the Ear, Nose, and Throat in Children. By T. G. Wilson, M.B., B.Ch., Litt.D., F.R.C.S.I., M.R.I.A., ear, nose, and throat surgeon, Dr. Steevens' Hospital, and ear, nose, and throat surgeon, National Children's Hospital, Dublin. 8°, cloth, 307 pp., with 145 illustrations. New York: Grune and Stratton, 1955. $12.00.

A Doctor's Book of Hours: Including some dimensions of the emotions. By Merrill Moore, M.D. 8°, cloth, 397 pp. Springfield, Illinois: Charles C Thomas, 1955. $6.00.

Handbook of Pediatrics. By Henry K. Silver, M.D., associate professor of pediatrics, Yale University School of Medicine; C. Henry Kempe, M.D., assistant professor of pediatrics, University of California School of Medicine; and Henry B. Bruyn, M.D., assistant professor of pediatrics and medicine, University of California School of Medicine, and assistant clinical professor of pediatrics, Stanford University Medical School. 24°, cloth, 548 pp., with 33 illustrations. Los Altos, California: Lange Medical Publications, 1955. $3.00.

L'Homéopathie. By Pierre Vannier. 24°, paper, 136 pp. Paris: Presses Universitaires de France. ("Que sais-je?"-*Le point des connaissances actuelles.)*

Ciba Foundation Colloquia on Ageing: General aspects. Vol. 1. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S., assisted by Joan Etherington. 8°, cloth, 255 pp., with 38 illustrations and tables. Boston: Little, Brown and Company, 1955. $6.75.

Management of Disorders of the Autonomic Nervous System. By Louis T. Palumbo, M.D., chief, Surgical Service, Veterans Administration Hospital, Des Moines, Iowa, and senior surgical consultant, Veterans Administration Hospital, Knoxville, Iowa. 8°, cloth, 186 pp., with 23 illustrations. Chicago: Year Book Publishers, Incorporated, 1955. $5.00.

Klinische Psychopathologie. By Prof. Dr. Kurt Schneider, professor, Universität Heidelberg. Fourth edition. 8°, cloth, 188 pp. Stuttgart: Georg Thieme, 1955. DM 12.80. $3.05. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Proceedings of the Third Medical Conference of Muscular Dystrophy Associations of America, Incorporated. New York, New York. October 8 and 9, 1954. 8°, paper, 324 pp., with illustrations, tables and charts.

Medical and Public Health Laboratory Methods. Edited by James Stevens Simmons, M.D., Ph.D., Dr. P.H., dean and professor of public health, Harvard School of Public Health; and Cleon J. Gentzkow, M.D., Ph.D., director, Bureau of Laboratories, Department of Health, Commonwealth of Pennsylvania. Sixth edition. 8°, cloth, 1191 pp., with 115 illustrations, 9 colored plates and 129 tables. Philadelphia: Lea and Febiger, 1955. $18.50.

Prolonged and Perplexing Fevers. By Chester S. Keefer, M.D., physician-in-chief and director, Evans Memorial, Massachusetts Memorial Hospitals, and Wade Professor of Medicine, Boston University School of Medicine; and Samuel E. Leard, M.D., assistant visiting physician and assistant member, Evans Memorial, Massachusetts Memorial Hospitals, and instructor in medicine, Boston University School of Medicine. 8°, cloth, 248 pp. Boston: Little, Brown and Company, 1955. $5.50.

Cardiology Notebook: For preliminary instruction in medical curricula: Columbia University College of Physicians and Surgeons. Edited by Alfred P. Fishman, M.D., chairman, et al. 4°, cloth, 96 pp., with 18 illustrations and charts. New York: Grune and Stratton, 1955. $2.50.

Collected Papers of The Mayo Clinic and The Mayo Foundation. Vol. 46 (1954). Edited by Richard M. Hewitt, M.A., M.D., et al. 8°, cloth, 843 pp., with 189 illustrations and tables. Philadelphia: W. B. Saunders Company, 1955. $12.50.

NOTICES

BOSTON UNIVERSITY SCHOOL OF MEDICINE, HARVARD MEDICAL SCHOOL, AND TUFTS UNIVERSITY SCHOOL OF MEDICINE

The departments of pharmacology of Boston University School of Medicine, Harvard Medical School and Tufts University School of Medicine will hold a seminar in the Lecture Room of Building C, 80 East Concord Street, Monday, February 27, at 4:30 p.m. Dr. George W. Kidder, Stone Professor of Biology, Amherst College, will talk on the subject "A Discussion of the Biologic Effects of Purine and Pyrimidine Analogs." Tea will be served in the Pharmacology Department, third floor, Building A, 80 East Concord Street.

PHI DELTA EPSILON LECTURE

The Aaron Brown Lecture of Alpha Omicron chapter of Phi Delta Epsilon Fraternity will be presented by Dr. Richard H. Sweet, who will speak on the topic "The Diagnosis and Clinical Characteristics of Mediastinal Tumors," in the auditorium of Building A, Boston University School of Medicine, on Tuesday, March 6, at 5 p.m.

ARTHRITIS CLINIC FOR OUTPATIENTS

The Robert B. Brigham Hospital — with complete facilities for the treatment and study of arthritis and other rheumatic diseases — announces the opening of an outpatient clinic on February 1 for the diagnosis and treatment of arthritic problems of both adults and children.

Regardless of ability to pay, all patients are seen by members of the active visiting staff, and in the outpatient clinic no professional fee is charged. A consultation clinic is also provided for private patients on a fee-for-service basis. A complete written report of the findings with diagnosis and recommendations will be sent to a referring physician at the earliest possible date.

All visits are *by appointment only*, which may be made by a telephone call to the Admitting Office (LOngwood 6-6966) or application in writing to the Robert B. Brigham Hospital, Parker Hill, Boston 20, Massachusetts.

NEW ENGLAND DIABETES ASSOCIATION

A meeting of the New England Diabetes Association, on the general topic "Current Research in Diabetes and Carbohydrate Metabolism," will be held in the Jimmy Fund Building, Children's Medical Center, 35 Binney Street, on Tuesday, March 1, at 8 p.m. The program is as follows:

Role of Glucagon in Regulation of Blood Sugar. Theodore B. Van Itallie, M.D.

Abnormal Glucose Tolerance in Pregnancy. Hugh L. C. Wilkerson, M.D.

Current Studies with BZ 55. Howard F. Root, M.D.

All interested persons are invited.

NEW ENGLAND SURGICAL SOCIETY

The spring meeting of the New England Surgical Society will be held at the Peter Bent Brigham and Children's hospitals, Boston, on Wednesday, April 4.

NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held on Wednesday, March 21. The morning and afternoon sessions will be held at Science Park Museum, Science Park, Boston. Dr. Allan M. Butler will act as host. At the evening meeting, which will be held at Longwood Towers, Dr. Allan Ross, professor of pediatrics, McGill University Faculty of Medicine, and physician-in-chief, Montreal Children's Hospital, will give a talk on the subject "The Infant and Child in the Hospital."

MASSACHUSETTS HEART ASSOCIATION

The fourth in the series of "Stump the Cardiologist" meetings sponsored by the Massachusetts Heart Association will be held in the Jimmy Fund Auditorium, Binney Street, on Wednesday, February 29, at 8 p.m. Dr. Howard B. Sprague will discuss and answer questions on the subject, "Management of Congestive Heart Failure."

Drs. Paul R. Withington and Joseph R. Frothingham will act as moderators.

MASSACHUSETTS GENERAL HOSPITAL

The fourth in a series of evening symposiums given by the Children's Medical Service of the Massachusetts General Hospital will be held in Amphitheater 3A of the White Building, Massachusetts General Hospital, Boston, on Wednesday, March 7, at 7:15 p.m. The subject will be "Too Tall, Too Short and Too Fat — Clinical Illustrations of Common Remediable Conditions Causing Abnormalities in Physical Growth."

All interested physicians are invited to attend.

MEDICAL AND DENTAL SYMPOSIUM

A medical and dental symposium for the armed forces has been scheduled for March 21, 22 and 23 on the topic "Developments in Military Medicine and Dentistry with Special Emphasis on Atomic Warfare, Special Weapons and Isotopes."

The meeting on the first day will be conducted at the U. S. Naval Hospital, Chelsea, Massachusetts. On the mornings of the second and third days clinics will be scheduled at various hospitals in Boston on the subject "Treatment of Diseases with Radioactive Isotopes." Afternoon lectures will be given at the Jimmy Fund Building and in the auditorium of the New England Deaconess Hospital.

Among the speakers are the Honorable Christian Herter, governor of the Commonwealth of Massachusetts; Frank Berry, M.D., assistant secretary of defense for health and medicine; Rear Admiral Bartholomew Hogan, MC, U.S.N., surgeon general of the Navy; Rear Admiral Ralph W. Malone, DC, U. S. N., assistant chief, Bureau of Medicine and Surgery for dentistry; Brigadier General Elbert DeCoursey, MC, U.S.A., commanding officer of the Army Medical Service School; Captain George M. Lyon, assistant chief medical director for research and education, Veterans Administration; Charles L. Dunham, M.D., director, Division of Biology and Medicine, Atomic Energy Commission; and Captain Shields Warren, MC, U.S.N.R., professor of pathology, Harvard Medical School, and, formerly, director of the Division of Biology and Medicine, Atomic Energy Commission.

Programs and additional information may be obtained from the District Medical Office, First Naval District, 495 Summer Street, Boston 10, Massachusetts. This symposium has been approved for retirement point credit for those in attendance who are on the Active Status List in the Armed Services Reserve Programs.

YALE UNIVERSITY SCHOOL OF MEDICINE

The Yale University School of Medicine announces that an Alpha Omega Alpha Lecture will be held at the Fitkin Amphitheater, Tuesday, March 13, at 8:15 p.m.

Dr. W. Barry Wood, Jr., will give a talk entitled, "An Experimental Analysis of the Defenses of the Host in Acute Bacterial Pneumonia."

COLLEGE OF MEDICAL EVANGELISTS POSTGRADUATE CONVENTION

The Alumni Postgraduate Convention of the College of Medical Evangelists will be held in Los Angeles, California, March 4-8. The convention will be open to all doctors of medicine regardless of their school affiliations. Scientific lectures and refresher courses will be offered. Advance programs will be sent by mail. Further information may be obtained from the Managing Director, Alumni Postgraduate Convention, 316 North Bailey Street, Los Angeles 33, California.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The American Academy of Dermatology and Syphilology announces the Earl D. Osborne Fellowship in Dermal Pathology, to provide annually the opportunity for study and training in dermal pathology, for a postgraduate student who has completed satisfactorily at least one year, and preferably two years, of training in dermatology. The stipend is $4,000 a year divided into four quarterly payments during the year's fellowship. The period of training will be spent at the Armed Forces Institute of Pathology, Washington, D.C., the appointment being subject to approval by the director of the Institute. The next available appointment begins on July 1, 1957. Further information may be obtained from Dr. Hamilton Montgomery, chairman of the Committee on Pathology of the American Academy of Dermatology and Syphilology, 200 First Street Southwest, Rochester, Minnesota.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 16. Massachusetts Trudeau Society. Page 297, issue of February 9.
FEBRUARY 16. Yale University School of Medicine. Page 242, issue of February 2.
FEBRUARY 16, MARCH 28 and APRIL 18. Greater Boston Medical Society. Page 208, issue of August 4.
FEBRUARY 17. New England Rheumatism Society. Page 297, issue of February 9.
FEBRUARY 20–22. Atlanta Graduate Medical Assembly. Page 1136, issue of December 22.
FEBRUARY 20, MARCH 5, 19, APRIL 2 and 16. Hartford Medical Society. Page 242, issue of February 2.
FEBRUARY 21. South End Medical Club. Page 297, issue of February 9.
FEBRUARY 21, 28, MARCH 6, 13, 20, 27 and APRIL 3. Boston City Hospital House Officers' Association. Page 297, issue of February 9.
FEBRUARY 22. Yale University School of Medicine. Page 297, issue of February 9.
FEBRUARY 27. Boston University School of Medicine, Harvard Medical School, and Tufts University School of Medicine. Page 347.
FEBRUARY 27. Benjamin Waterhouse Medical History Society. Page 241, issue of February 2.
FEBRUARY 29. Massachusetts Heart Association. Page 347.
FEBRUARY 29, MARCH 21 and APRIL 25. Massachusetts Heart Association. Page 623, issue of October 6.
MARCH 1. New England Diabetes Association. Page 347.
MARCH 4–8. College of Medical Evangelists Postgraduate Convention. Page 347.
MARCH 5 and APRIL 2. Fried Lecture Series. Page 535, issue of September 22.
MARCH 6. Phi Delta Epsilon Lecture. Page 347.
MARCH 7. Massachusetts General Hospital. Page 347.
MARCH 15–17. American Orthopsychiatric Association. Page 86, issue of January 12.
MARCH 18. Yale University School of Medicine. Page 347.
MARCH 19–22. American Academy of General Practice. Page 1092, issue of December 15.
MARCH 19–28 and JUNE 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
MARCH 21. New England Pediatric Society. Page 347.
MARCH 21 and APRIL 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
MARCH 21, 22 and 23. Medical and Dental Symposium. Page 347.
MARCH 24 and 25. American Psychosomatic Society. Page 260, issue of August 11.
APRIL 3. Third Microcirculatory Conference. Page 139, issue of January 19.
APRIL 4. New England Surgical Society. Page 347.
APRIL 23–26. International Academy of Proctology. Page 86, issue of January 12.
MAY 2. Postgraduate Medical Institute. Page 487, issue of September 15.
MAY 3–5. American Goiter Association. Page 348, issue of August 25.
MAY 28–JUNE 1. European Symposium on Vitamin B. Page 578, issue of September 29.
JUNE 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.
JUNE 21–24. American Academy of Dental Medicine. Page 994, issue of December 1.
AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.
SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 10–14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 23

THURSDAY, FEBRUARY 23
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:15 a.m. Thoracic Conference. The Clinical Application of Pulmonary-Function Studies. Dr. John B. Petter. Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, FEBRUARY 24
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham. Auditorium, Carney Hospital, Dorchester.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, FEBRUARY 25
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
*10:30 a.m. Combined Medical-Surgical Rounds. Second and Fourth (Harvard) Medical Services. Dowling Amphitheater, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, FEBRUARY 27
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Medical-Pathological Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

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